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CONJOINED TWINS—FURTHER OBSERVATIONS

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The occurrence of conjoined twins is so rare that few single individuals have an opportunity of studying more than one example, but since the conjoined twins of Kano (Aird, 1954) were reported it has happened that we have had an opportunity of collecting a small series, and it seems desirable that such additional information as has emerged from it should be briefly put on record.

The title "conjoined twins" seems preferable to such alternatives as "craniopagus," "thoracopagus," "ischiopagus," and so on, because it standardizes the index of the titles of papers and ensures that no titles will be misplaced by those who prepare the great medical indexes.

Since the conjoined twins of Kano, which are referred to above, I have had an opportunity of examining two sets of living twins. The first of these was the Keighley twins, who were so extensively joined at the vertex that operative separation proved impossible, though the brains were separate. Franklin, Tomkinson, and Rohan Williams (1958) report that six craniopagus twins have been recorded in the available literature since 1949, but to these can be added the Keighley twins (which were not recorded in medical literature), and a craniopagus born in Homburg in the early 1950's and illustrated at the age of 3 years in the weekly journal *Neue Illustrierte*. In these German twins there is very extensive bilateral parietal conjunction, and the heads are rotated on each other in such a way that the two left eyes are virtually in line. An unsuccessful attempt was made in the case of these twins to narrow the area of conjunction by increasing pressure of a circular nylon band. In the case of the Keighley twins the sagittal axes diverged also, but only slightly, and in the craniopagus recorded by Franklin *et al.* (1958) the cranial axes are said to be at right angles.

At the kind invitation of Dr. Wijthoff, who delivered the babies, and Dr. Straat, who performed the operative separation, I was permitted to examine and to see the operation performed upon the Dutch twins of Leeuwarden. They were joined between umbilicus and xiphoid process by a tube of skin and a narrow bridge between the two livers.

Particulars of Four Stillborn Pairs

In addition to these we have had an opportunity of examining four pairs of stillborn twins. What was clear in these was that the degree of conjunction of internal organs varies fairly accurately with the extent of external union if the junction is median.

The first specimen, very kindly provided by Mr. N. Alders and Dr. T. K. Owen, showed externally a conjunction from the umbilicus to the lower part of the sternum. In these twins the thoracic organs showed no conjunction, nor did the stomachs, but the enteric canal was single from the middle of the duodenum to a point on the ileum where one might have expected to find a Meckel's diverticulum—in fact, to the level of the vitelline duct and therefore to the umbilicus. It is of interest that in this case an antenatal diagnosis of conjunction was made by Dr. R. McK. Crichton on the grounds that the *x*-ray films showed the twins facing each other, the chests closely approximated, and the vertebral columns in a position of exaggerated lordosis.

The second example, kindly sent to us by Mr. J. F. Foulkes, showed external conjunction from the manubrium sterni on each side to a common umbilicus. The external organs manifested a complexity that would have been quite incompatible with surgical separation. Each half of the thoracopagus was provided with a pharynx, larynx, and upper trachea. In the highest point of external conjunction the trachea and oesophagus on one side joined with that on the other to form a single tube, proceeding through a joined diaphragm to reach a single stomach, which in turn emptied into a single jejunum, but the ileum again branching at the site of a single Meckel's diverticulum to pass separately on each side into a normal caecum. The liver was extensively joined, the plane of conjunction running obliquely, so that surgical division of the liver, had it been attempted, would have transected on both sides biliary and venous channels. A single heart was situated in the thorax of one of the twins, and from it two separate aortas proceeded asymmetrically to provide a circulation, one aorta for each side. The arrangement of the cardiac chambers and of the great veins was extremely complex and has not yet been fully analysed. A curious feature, when one remembers that lung alveoli bud out from growing bronchi, was the appearance in the thoracic cavities of a number of separate and isolated patches of collapsed lung tissue which might have been taken for bronchial pulmonary segments.

The third case, provided by Dr. Vivienne Croxford with a prenatal diagnosis by Dr. Ethel Pepper, was that of a conjunction that extended from the mouth to the umbilicus. The whole gastro-intestinal tract was single, and in other respects the organs followed the pattern just described.

The fourth example was provided by Professor J. M. Browne in this hospital. It closely resembled the first of the specimens mentioned above.

In the first and third cases the prenatal diagnosis was not communicated to the parents, the presumption being that the twins would be born dead. This seems a humane rule to follow.

Origin of the Condition

There are very strong reasons for assuming that most, if not all, conjoined twins are uniovular in origin. The grounds for this belief are as follows: (1) Conjoined twins nearly always unite at nearly identical parts of their external surfaces. Probably the great majority of deviations from this rule are relatively minor degrees of torsion or of stretching of the twins *vis-à-vis* each other. This would, for example, explain the slight asymmetry of the axes of craniopagus twins. (2) Conjoined twins are nearly always obviously of the same sex, and are never of opposite sexes. (3) A fairly full genealogical table is available of the descendants of the original "Siamese" twins, Eng and Chang Bunker. These twins are estimated to have had more than 1,000 descendants in the United States of America and twins did not appear again in the family until a few years ago, four generations after the original brothers. These last twins were apparently uniovular, but separate and normal. This very low incidence of twinning in the family very nearly excludes a binovular origin.

The nature of the initial fault is not yet certain. As Hamilton (1954) first suggested, the phenomenon could be explained by the assumption that monovular twins develop, as they do in some other genera, by what is for these genera a normal method of propagation, symmetrical division of the embryonic area of the blastocyst, separation remaining incomplete when conjunction occurs. Fairly strong evidence that conjoined twins arise in an abnormality in one germinal area is the fact that very often one or other of the twins, or both, bear supernumerary rudimentary limbs.

The alternative explanation may be that uniovular twinning is due to the development of two separate embryonic axes in the same blastocyst. Conjunction would then depend upon the overlapping to a varying extent and the fusion of the two axes over an area of varying extent.

The possibility, however, that in at least a few cases conjunction is determined by the fusion of two separate blastomeres cannot be entirely ruled out, though it would require two separate abnormal embryological events: first, rupture of the amniotic partition (nearly all, or perhaps all, conjoined twins lie in a single amniotic sac), and, secondly, a fusion of the embryos. Such a fusion of genetically different embryological tissues would theoretically not be impossible. There are one or two exceptional circumstances which may indeed point to this kind of origin.

1. Conjoined twins are not identical in the same degree as separate uniovular twins. Differences of feature, of stature, and of temperament are nearly always detected. Indeed, the differences between the original "Siamese" twins, Chang and Eng Bunker, were actually caught by a contemporary English political cartoonist, who used a drawing he made of them to illustrate his conception of the bloated capitalist inescapably tied by circumstances to his inebriate wage-slave brother.

2. Conjunction of extensive degree is very commonly associated with asymmetry in the internal organs. We have had one example of a single asymmetrical heart and one example of dextrorotation of the heart, and other misplacements of viscera are frequent.

3. Endocrine asymmetry sometimes occurs too. In the case of conjoined twins previously reported (Aird, 1954) the twin who died after operation had less than her share of adrenal tissue, and her sudden death was suggestive of acute adrenocortical insufficiency. In the case of the Leeuwarden twins the pulse rate after operation showed a rapid and rather anxious rise with a fall in blood pressure which was corrected by hydrocortisone.

4. An example has been brought to our notice of an even more remarkable endocrine disturbance. The late Major Southwell Oliver provided me with a photograph of adult Chinese twins joined at the pelvis. One of these twins is a normal-looking Chinese adult male of rather handsome appearance, while the other has the slight obesity, the chubby hands, and the features of a eunuch. This twin is taller and heavier than his brother, with characteristically broad shoulders. The precise below- and above-waist ratios in these twins are difficult to estimate, for they are dressed, but it is clear that this ratio in the case of the eunuchoid twins is of characteristic eunuchoid type with long legs and a relatively shorter body. I am informed that the eunuchoid twin had no detectable testes. This seems a very remarkable example of conjunction, and strongly suggests a freemartin phenomenon. I understand that a true freemartin has not been described in man, and this photograph would thus seem to be of historic importance. If my interpretation of the photograph is correct this must be an example of the development of conjoined twins by the union of initially separate blastomeres. The rarity of this situation, and the almost invariable equality of sexes in conjoined twins, strongly suggest that all but the very smallest possible minority of conjoined twins are uniovular.

The Chinese conjoined twins.

5. I have said that in the great majority of cases conjoined twins are united by similar points of their anatomy. Nevertheless, occasionally conjunction is duplicated. The original Biddendon twins are said to have been joined at the hip and at the shoulder, and in pictorial representation they are usually delineated as having precisely that double junction. We have recently had an opportunity of treating surgically a baby patient whose case will be reported in great detail later (Aird and Gavourin, unpublished data). To this child was attached a teratoma which was provided with a peritoneal cavity in continuity with his own, pelvic colon and rectum, and two lower limbs. The teratoma was attached to the host at two separate points—lower abdomen and peritoneum. Other examples of duplicated "conjunction" are on record. It is conceivable, of course, that germinal areas in a single blastomere might overlap and fuse at two separate points, but other explanations are nevertheless possible. Twins fused primarily at one area might conceivably obtain a secondary fusion later, or separate blastomeres might conceivably become attached to each other at two different points.

Discussion

While it is admitted that the weight of evidence points to the great majority of conjoined twins deriving from a single blastomere, the considerations which I have enumerated above should at least keep our minds open to the possibility of a union between separate blastomeres. It would seem desirable to test the blood of conjoined twins for chimerism (the blood changes consequent upon the possession of blood-forming tissue of different types, such as binovular twins of different blood group have sometimes if their placental circulations have communicated). The demonstration

of a chimera would very strongly suggest, though its absence would not of course disprove, an origin from two separate ova and its presence might depend upon a third separate (and binovular) twin.

There have been several recent interesting reports of conjoined twins. Franklin *et al.* (1958) have recorded a craniopagus, and mention that this is the sixth recorded since 1949. This figure obviously does not include the Keighley twins, for these authors state that the last case known to have been born in England was that of Cameron (1928), and it is unlikely to include the Homburg twins, for I do not think these have been described in the literature. Stiggelbout (1958) records stillborn macerated conjoined twins in Kaduna, Nigeria, and notes the relative prominence of that country in the history of conjoined twins. He mentions the twins which I reported earlier (Aird, 1954) and the Port Harcourt twins reported by Roddie in 1957. In fact, Nigeria has been even more prolific of surviving conjoined twins. McLaren (1936) recorded successful separation of conjoined twins born to a Hausa woman in Sokoto, Nigeria, and they are still surviving. In addition to these were the stillborn twins recorded by Bowesman (1940). The survivor of the Nigerian twins that I separated in 1953 is alive and well, a very bright child, normal physically and mentally. Unfortunately her mother died of a placenta praevia in 1957.

The history of the separation of twins can now be fairly clearly documented. The first successful operation was that performed by Professor Doyen in 1902 in Paris for the separation of the Radica-Doodica sisters, one of whom had developed abdominal tuberculosis. The tuberculous sister died but the other survived. It is notable that Professor Doyen had a cinematograph film made of the operation, and by courtesy of the editor of the *Nursing Mirror* I have a copy of a print of two of the frames from the film. This film preceded the opening of the first public cinema theatre by about two years, though it was not the first example of the use of a motion-picture camera in the operating theatre. I am told that Professor Doyen was accused of having shown this film to the general public for profit, and felt impelled to vindicate his honour in a duel.

The second successful separation was done in October in 1912 in the Military Families Hospital at Portsmouth by an unnamed R.A.M.C. officer; one of these twins died four months later, but the other survived and was well in 1954, though we have since lost sight of her.

The third successful operation was that done by Dr. Holm, of Minnesota, on January 8, 1927, and the fourth was by Dr. D. W. McLaren (1936) in Nigeria.

Summary

Some account is given of three sets of living conjoined twins and four stillborn pairs of conjoined twins that have come to our attention.

A possible instance of a freemartin effect in human conjoined twins is illustrated.

The arguments for a monovular origin for the very large majority of conjoined twins are presented, but it is suggested that conjunction may really be due to the union of binovular germinal areas, and it is suggested that chimerism should be sought in conjoined twins.

I am grateful to all my colleagues who have provided me with the material and data on which this report is based. To the names of those to whom we are indebted mentioned in the text must be added Dr. C. Bowesman, Professor J. McC. Browne, Brigadier J. Houston, Dr. A. D. J. Farquharson, Captain Gavourin, Dr. G. F. Longbotham, Mr. Hujohn Ripman, Dr. J. Rooth, and Dr. A. O. Sasegbon.

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BREAST CANCER

A NEW APPROACH TO THERAPY

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[WITH SPECIAL PLATE]

The best results of surgery and radiation in the treatment of breast cancer show no grounds for complacency, and it is difficult to foresee that any spectacular improvement will come from existing methods which assume that the disease in the early stages is localized to the breast and adjacent lymph nodes. The condition, even when apparently early, may already be beyond effective reach of contemporary treatment, since Cade type 1 patients with a carcinoma in an outer quadrant commonly show involvement of the internal mammary lymph-node chain and presumably more distant sites, and in types 1 and 2 tumour-cell emboli are already being disseminated, particularly during surgery. Goodall (1958) draws attention to the frequency with which the ovary is involved in patients supposedly type 2.

At present the prognosis is largely one of conjecture. A woman under 30 is almost certainly doomed within a year, especially if her breast cancer arises in association with pregnancy or lactation. In the woman of 65 or more prognosis is relatively favourable, but between these ages the outlook is completely uncertain save in the known advanced case. Recent work involving endocrine ablation offers further prospects in the late breast cancer, but even with such radical measures as pituitary ablation or bilateral adrenalectomy with oophorectomy, positive palliative results are obtained only in approximately 50% of cases, and a good remission lasting for a year or longer in rather less than 25% (Illingworth, 1958).

A similar remission in a minority of women in any age group may be obtained with androgen therapy, especially when the symptoms are due to bony metastases (Martin and Hynes, 1954). Eventually, irrespective of the nature of the endocrine therapy employed, the tumour ceases to respond and death of the patient inevitably follows. This is due to an apparent change in the growth pattern of the neoplasm from one of endocrine, presumably oestrogen, dependency to a truly autonomous type, and may arise from a selective breeding out of the oestrogen dependent cells under endocrine therapy. It occurred to us that it should be possible to prevent the emergence of the

endocrine-resistant strain of cancer cells by the simultaneous administration of an antimitotic drug. The antimitotic drugs, notably the alkylating agents, have been used with considerable success in the therapy of the reticuloses (Wilkinson, 1953). It is rather surprising that few systemic trials of these agents have been made in the solid cancers.

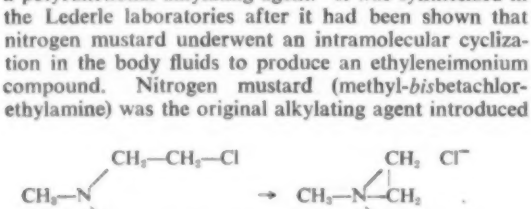
It is reasonable to assume that during the process of metastasis the tumour cells are more susceptible to antimitotic agents and endocrine therapy than later, when the metastases have already become established in distant organs. It would appear logical to begin systemic therapy as soon as possible after diagnosis in view of the tendency of breast cancer to disseminate early. Patients with Cade type 2 cancers as well as those with more advanced cancers were therefore admitted to the trial.

It was decided, for the sake of simplicity, to use testosterone with oophorectomy as the endocrine part of the therapy. "Thiotepa" (triethylene thiophosphoramide) was chosen as the alkylating agent after Personeus *et al.* (1952) had shown that it had an effect against metastasizing mammary carcinoma in the rat. Shay *et al.* (1953) and Bateman (1955), in trials of thiotepa in a variety of advanced human cancers, showed that the drug had some selective action in human breast cancer. The object of this paper is to report on the preliminary results obtained by combining endocrine therapy with the administration of an antimitotic agent.

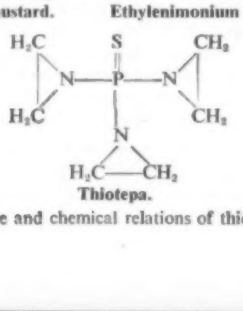
Chemistry and Pharmacology

The chemistry and physiological actions of testosterone are well known and need not be described in detail here. It should be noted, however, that apart from its androgenic effect, testosterone has a marked protein anabolic action in the body and tends to stimulate haematopoiesis. This latter action of the hormone influenced our choice of this particular method of endocrine therapy, as it was thought possible that it might help to counteract the undesirable marrow-depressant action of thiotepa. It is thought that its action in breast cancer is due to the androgenic effect rendering the environment unsuitable for the further growth of an oestrogen-dependent tumour. It is not believed to have any direct cytocidal effect.

Thiotepa (NN′N″—triethylenethiophosphoramide) is a polyfunctional alkylating agent. It was synthesized in the Lederle laboratories after it had been shown that nitrogen mustard underwent an intramolecular cyclization in the body fluids to produce an ethyleneimonium compound. Nitrogen mustard (methyl-*bis*betachlorethylamine) was the original alkylating agent introduced



Nitrogen mustard. Ethylenimonium transformation.



Thiotepa.

Structure and chemical relations of thiotepa.

by Wilkinson and Fletcher (1947) for the treatment of the reticuloses. The chemical relationship of thiotepa to nitrogen mustard is shown in the formulae.

The antimitotic action of the alkylating agents has been ascribed to a cross-linkage which occurs between the two or more functional groups — that is, the ethyleneimino radicles of the agent and two homologous centres in the dividing chromosomes. Such an action causes severe disruption of mitosis with fragmentation and disorganization of the chromosomes. These cytological effects have been described by Koller (1958). Thiotepa is therefore a direct-acting cytocidal agent.

Apart from the other considerations mentioned in the introduction, the advantages of using testosterone and thiotepa are obvious, as each drug inhibits cancer growth by a different method.

Thiotepa: Preparation and Administration

The dry crystalline powder was dissolved in sterile distilled water to give a concentration of 5 mg./ml. It was sterilized by filtration through a sintered glass filter and stored at 5° C. The solution was used within 10 days of preparation.

The intramuscular route of administration was used in all patients. In the 11 patients who received thiotepa alone, 15 mg. of the drug was given two or three times a week until the white-cell count fell below 3,000 per c.mm. Therapy was then interrupted, being recommenced only when the blood count had returned to pre-treatment levels. In the remaining 23 patients who received testosterone in combination with thiotepa the individual dose of thiotepa was eventually increased to 30 mg. on alternate days until a total dose of between 180 and 300 mg., depending on the response and blood counts, was given. At the completion of this course the patient was rested for an interval of three to six weeks, and then a further similar course of therapy was administered.

In some patients, after a lapse of one month, a third course was given; others were placed on a maintenance dose of 15–30 mg. of thiotepa at intervals varying between two and four weeks.

Testosterone was administered by intramuscular injection, 200 mg. of testosterone propionate being given five times a week, beginning one week before the course of thiotepa and continuing for two weeks after completion of the thiotepa injections.

Six patients with pleural and peritoneal effusions had thiotepa 30 mg. in 30 ml. of normal saline instilled direct into the cavity after paracentesis. This was in addition to their normal course of intramuscular injections. In only one patient was direct injection into a recurrent tumour mass in the scar tissue of the chest wall attempted. Difficulty due to the tough fibrous tissue was experienced in efficiently carrying out the injection, and this route of administration was subsequently abandoned.

Daily blood counts were carried out during the course of treatment. If the total white-cell count fell below 2,000 the thiotepa injections were temporarily stopped but the hormone therapy was continued.

Adjuvant Therapy

Any patient whose haemoglobin level was 10 g./100 ml. or below was transfused with concentrated cells. Transfusions during the course of therapy were

given if a patient's haemoglobin fell below 10 g./100 ml. Cortisone, 100 mg. daily, was given to three patients who developed thrombocytopenia with extensive purpura during therapy. This hormone was withdrawn after the purpura cleared up. In two patients with massive oedema of the arm on the affected side, systemic hyaluronidase was administered, using "varidase" buccal tablets.

Simple mastectomy, using diathermy, in 11 previously untreated cases was carried out. In three patients this was performed at the onset of treatment in order to verify the diagnosis, and in eight it was carried out in the interval between the first and second courses of thiotepa or after a varying period of time after completion of the second course. An injection of 30 mg. of thiotepa was given at the time of operation to these patients to take care of any viable tumour emboli liberated into the blood stream by the operative procedure. Oophorectomy was performed on those patients who were still within the menarche.

Selection and Assessment of Patients

Initially only those patients with widely disseminated lesions, or who had recurrences after radiation or surgery, were admitted to the trial. Subsequently, when the efficacy of the treatment was established, we took any patient with a carcinoma of the breast irrespective of the stage of the disease. In each patient the diagnosis of breast carcinoma was confirmed by histological examination of the specimens obtained from either biopsy or simple mastectomy.

Before therapy was begun a complete clinical assay by two independent observers was made. This included a radiological study of the skeleton and chest and the following pathological investigations: a complete blood count, estimations of E.S.R., C-reactive protein concentration, plasma proteins and the electrophoretic pattern, blood uric acid level, alkaline phosphatase, and 24-hour urine calcium outputs. These investigations were repeated from time to time during the course of treatment and follow-up.

Clinical Material

The group consists of 34 patients whose ages range from 23 to 76 years. At the beginning of therapy 17 patients were still within the menarche. In four of the remainder the growth had begun during the menarche. One patient, aged 23 years, was pregnant. Eighteen patients had recurrent lesions or metastases following previous surgical or radiation therapy. In four of these the recurrence began between three and seven years after their original treatment and in the remaining 14 within three years. Sixteen patients had had no previous treatment: seven of these were clinically Cade type 2, although this staging was subsequently altered in two after the discovery of microscopic secondaries in the ovaries at oophorectomy. The remaining nine previously untreated patients had advanced cancers with metastatic lesions in the viscera and skeleton.

The known duration of the cancer prior to chemotherapy ranged from nine months to over eight years in the previously treated group, and from two months to two years in the untreated group. The frequency and nature of the metastatic lesions are summarized in Table I.

In two patients the primary growth was a papillary duct carcinoma. In four others the tumours were graded histologically as poor to moderately differentiated adenocarcinoma. The remaining 28 tumours encountered were anaplastic, six, including the pregnancy carcinoma, being of the richly cellular medullary type, while 22 were of the scirrhous variety.

Results

Assessment

All patients were examined at fortnightly intervals and their progress was recorded. Where possible any change in the size of the tumour masses, hepatomegaly, etc., was recorded in centimetres. Serial *x*-ray studies, using a standardized technique, were made of the skeletal and lung metastases. Serial estimations of E.S.R., C-reactive protein concentration, concentration of the alpha-globulins, haemoglobin concentration, and patients' weights were found helpful in evaluating the regression of widespread disease. The effect of treatment on skin ulcers was recorded photographically. Eight patients were submitted to mastectomy at varying intervals during therapy, and in them the results of therapy could be assessed histologically. The 24-hour urinary calcium output was of value in following the progress of the skeletal metastases.

Remission Frequency and Duration

The effects of treatment in the various lesions encountered in the group are recorded in Table I.

TABLE I.—*Response of Lesions to Chemotherapy*

Nature and Site of Lesion	No. of Patients	Regression	Partial Regression	No Response
Primary tumour ..	16	11	3	2
Skin ulcer	10	6	3	1
Soft tissues } ..	18	14	2	2
Lymph nodes }				
Lungs	8	5	2	1
Pleural effusions ..	6	2	2	2
Liver	8	4	2	2
Ascites	5	2	—	3
Skeleton	11	7	1	3
Brain	3	0	1	2

Lesions showing marked or moderate regression by the above criteria are grouped together in the column marked "regression." Lesions which ceased to progress or which diminished slightly during the period under observation are grouped together in the column marked "partial regression." Lesions which failed to show any response and which continued to increase in size are placed in the column marked "no response." The age of the patient and her endocrine status—that is, whether she was within the menarche or post-menopausal—did not seem to influence the extent or rapidity of the response. With the possible exception of the papillary duct carcinomas, no correlation was found between the histological type and the response to treatment, and as there were only two papillary carcinomas in the group, both very advanced, this exception may be fortuitous. The site of the lesions did not influence response.

All the metastases in a patient either showed evidence of regression or else no response was obtained, but it was found that certain sites, notably skin and primary tumours, responded earlier than others. Regression of tumour growth was obtained in 8 out of the 11 patients treated with thiotepa alone and in 22 out of 23 patients receiving thiotepa and testosterone. Four patients failed to show any response and died within four weeks of commencing therapy. They included two patients with cerebral metastases and the only two papillary duct

TABLE II.—*Remission Rate and Duration*

Cade Typing	No. of Patients	Remissions Obtained	Duration of Remission (Months)		Deaths
			Average	Range	
Previously Untreated					
2	7	7	8·0	5–13	0
3 and 4	9	8	9·5	2–19	3
Previously Treated					
Local recurrences	6	6	15·3	4–26	0
Distal metastases	12	9	13·4	2–19	5

carcinomas in the group. Table II shows the average duration of the remission obtained in the series in relation to the stage of the disease at the beginning of treatment. It should be noted that, apart from four patients, the initial remission was still present in the remainder of the group at the time of writing.

Survival Time

Apart from the four deaths noted above, four other patients died after a period in which the progress of the disease was arrested. Two were treated with thiotepa alone, but after periods of two and five months respectively, during which tumour regression was obtained, the drug had to be discontinued owing to the severe marrow depression. Both patients relapsed and died as a result of their metastatic lesions within three months. One other patient was apparently free of symptoms from her carcinoma but died out of hospital from influenzal bronchopneumonia. The remaining death was that of a patient whose history and post-mortem findings are given in detail below (Case 2).

Subjective Results

Those patients who showed regression of the tumour growth experienced marked subjective improvement in their sense of well-being. Symptoms such as pain, anorexia, and anxiety or mental apathy disappeared. They gained weight, and where anaemia had been present this disappeared. Non-specific tests such as the E.S.R. returned to normal.

Objective Results

1. *On Skeletal Metastases.*—Eleven patients had metastatic deposits in the skeleton ; all except one were of the osteolytic character and were associated with considerable pain. Four had pathological fractures and three were bedridden from spinal metastases. Eight patients responded to treatment. Three bedridden patients became ambulant and returned to a normal life. The response in this group was very impressive, as before treatment all these patients had to have pain-relieving drugs and after therapy these drugs could be discontinued. In patients responding to treatment a characteristic sequence of events was noted. For a short period of approximately one to two weeks' duration bone pains appeared to be aggravated, and, if the affected bone was superficial, redness and oedema were noted in the overlying skin and soft tissue. Subsequently the pain and the local signs disappeared. There followed a lag period of between six weeks and three months during which serial *x*-ray films revealed no further progress in the extent of the bone lesions but no evidence of recalcification. During this period the 24-hour urinary calcium output, which at the beginning of therapy was usually above 300 mg., returned to normal (less than 300 mg.). The high serum alkaline phosphatase concentration and C-reactive protein levels also tended to drop. In the third and final stage recalcification was noted radiologically in the skeletal metastases and the serum alkaline phosphatase tended to rise but the C-reactive protein test became negative. Fig. 1 (Special Plate) shows a pathological fracture of the humerus before and during treatment.

2. *On the Primary Tumour.*—In 16 patients the primary growth was present at the beginning of therapy, and in some of these the involved breast, owing to the extent of the growth and oedema, was at least two to three times the size of the normal breast. Recession could therefore be easily assessed. Diminution in size was noticed to begin within two weeks of completion of the first course of therapy. Shrinkage often continued to the point where the affected breast was smaller than the unaffected one. This usually occurred within four to six months. In two patients with small primary tumours the growth disappeared completely to palpation in six weeks. In five patients the tumour had ulcerated the skin. Healing of such ulcers began with the shrinkage of the tumour and was usually complete within two months of beginning treatment. In two patients the primary tumour showed no response to treatment.

3. *On Other Superficial Soft-tissue Lesions.*—These consisted of axillary lymphadenopathy, skin ulcers, and recurrent nodules in mastectomy scars. Except for the two patients with carcinoma of the papillary duct these lesions softened and regressed rapidly under treatment. One patient had a massive carcinomatous infiltration of the skin and soft tissues of the neck, which had developed three years after mastectomy and radiation therapy. The effect was to cause considerable pain, torticollis, and oedema. Complete clinical regression was obtained within six weeks of starting treatment. A successful local response to systemic therapy is illustrated in Fig. 2 (Special Plate). It was noted that patients who had had previous *x*-radiation with recurrence responded much more slowly to treatment than others.

4. *On Viseeral Secondaries.* — Nine patients with metastases involving the lungs, liver, and abdominal cavity were treated. In four patients no response was obtained. With the others, arrest of the progress of the lesions and regression in their size for periods varying at the time of writing from 2½ to 13 months have been obtained. Where pleural or peritoneal effusions were present inhibition of their formation was obtained. It was noted that lung secondaries appeared much more sensitive to the drug than liver secondaries and responded earlier.

Histological Response

The changes found in the breast tumours appeared to be related to the total amount of thiotepa administered and the duration of treatment prior to mastectomy. The earliest changes—that is, those found in tumours removed within two weeks of completion of the first course—consisted of intracellular oedema with hydropic degeneration of the nuclei and interstitial haemorrhages. Cells in mitosis showed abnormalities of the mitotic figures, notably clumping and fragmentation of the chromosomes.

The next stage was characterized by changes in the naked-eye appearances of the tumour. The customary "unripe pear-like" texture of the cut surface was

replaced by a mottled yellow appearance and the tumour felt much softer. Histological examination showed multiple areas of advanced coagulation necrosis (Special Plate, Fig. 3). The final stage was observed in one specimen removed six months after the beginning of treatment. In this the tumour was replaced by interlocking strands of dense fibrous tissue showing some blood pigment but no tumour cells.

In three patients the breast tumour was a recurrence which followed previous radiation therapy, and in these the degenerative changes were much less marked after chemotherapy. It was not unusual to find islands of apparently viable tumour cells in such growths. This finding is in agreement with the clinical impression of the slowness of response to chemotherapy in post-radiation recurrences.

Haematological Changes

Haematological tolerance varied with the individual often in an unpredictable manner. It was noted, however, that patients with multiple liver secondaries or those with leucoerythroblastic anaemia due to marrow secondaries showed a reduced tolerance. Patients previously treated with *x*-radiation also seemed more susceptible to the marrow-depressive action of thiotepa. Allowing for these factors, there appeared to be a difference in the tolerance of the group receiving thiotepa compared with the group receiving testosterone and thiotepa (see Table III). This table is based on the blood changes induced by the first course of therapy in each group. The very much higher total dosage of thiotepa in group 2 reflects an apparent increased resistance of the bone marrow to thiotepa in this group.

TABLE III.—*Leucopenia Following the First Course of Thiotepa*

Group Receiving	No. of Patients	Dose of Thiotepa mg. kg.		Max. Fall in W.B.C. % of Initial Count		Period to Recovery Days	
		Average	Range	Average	Range	Average	Range
1. Thiotepa alone ..	11	2·1	0·9–3·6	57	35–90	13	4–*
2. Thiotepa and testosterone	23	3·1	1·8–6·0	55	0–87	11·6	5–31

* In two patients the W.B.C. failed to recover before death.

In each group the lymphocyte count was the first to be depressed; this was followed by a depression of the granulocyte count and later, in a few patients, by the platelet count. Severe thrombocytopenia causing purpura occurred in five patients; three of these had received thiotepa alone. Treatment had to be abandoned permanently in two patients owing to severe marrow depression. Both these belong to group 1 of Table III. A slight eosinophilia was occasionally noted in patients responding to treatment. It was noticed that haematological tolerance was reduced slightly during the second and subsequent courses of therapy. Patients responding favourably to therapy usually maintained their haemoglobin levels and often showed a spontaneous rise. Depression of the red-cell count which could be directly attributed to the action of thiotepa was seen in only the two patients in group 1 who experienced the severe marrow depression.

Side-effects and Complications of Treatment

The depressive action of thiotepa on the bone marrow was the most serious complication encountered. A surprisingly small percentage of the patients (33%) showed marked hirsutism despite the massive dose of testosterone used. Increased libido was encountered in one patient. Less than 25% of the group complained of nausea following the thiotepa injections, and in these the nausea could be controlled with chlorpromazine or dimenhydrinate.

Case Histories

The clinical course and pathological findings in the following two cases, being of special interest, are recorded in detail.

Case 1

A 23-year-old woman first noticed a lump in the breast eight weeks after she had finished nursing her second child. She was seen at the clinic two weeks later. There was then present a diffuse tumour occupying practically the entire breast with an associated axillary lymphadenopathy. Simple mastectomy and oophorectomy were performed. Histological examination of the breast tumour showed the presence of an encephaloid anaplastic growth with numerous mitotic figures. Radial sections taken from the periphery of the breast revealed multiple tumour emboli in the lymphatics and smaller blood vessels. At oophorectomy the uterus was thought to be slightly enlarged. Therapy with testosterone and thiotepa was begun immediately the histological diagnosis was known. Two weeks after the completion of the first course (total dose of thiotepa 200 mg.) the axillary lymphadenopathy had disappeared.

Six weeks later the patient was admitted to hospital for the second course of treatment; she was then found to be pregnant. Radiographs of the abdomen showed a foetus of approximately four months. The pregnancy was terminated by hysterotomy. Dissection of the foetus revealed no significant abnormality; it was apparently a male infant. Haematopoiesis appeared to be occurring normally. The patient received a second course of thiotepa, total dose 200 mg., and four weeks later a third course of 270 mg. She was subsequently given a maintenance dose of 30 mg. of thiotepa with 200 mg. of testosterone once a month. At the time of writing, 12 months after the mastectomy, the patient was very well and was carrying out her duties as a housewife and mother of two young children. There was no clinical or radiological evidence of secondary growth. Her blood sedimentation rate, serum alkaline phosphatase concentration, C-reactive protein, blood count, and liver-function tests were all normal.

Case 2

This patient, aged 53, when first seen had multiple secondaries in the lungs, liver, and peritoneal cavity from a moderately differentiated adenocarcinoma. Oophorectomy was performed and at laparotomy the presence of the liver and peritoneal metastases was confirmed by biopsy. She was given three courses of thiotepa and testosterone injections, the total amount of thiotepa administered being 730 mg. Within four weeks of the first course it was apparent that the progress of the disease was arrested and the patient's general condition much improved. She gained weight. Hepatomegaly disappeared and there was a simultaneous softening and shrinking of the primary tumour and axillary glands. She maintained her improvement for three months; subsequently a rapidly progressive jaundice developed with a generalized anasarca. Biochemical tests then indicated a severe degree of liver failure. The patient died in hepatic coma.

At post-mortem examination multiple areas of necrotic tumour tissue were found at the sites of the previous metastases. Apparently viable cancer cells could be identified with certainty in some of the para-aortic lymph nodes. The lung secondaries had regressed completely. No

viable tumour cells were found in the liver, but this organ showed extensive areas of liver-cell necrosis and regeneration, with proliferation of bile ducts and fibroblasts. The appearances were those of an early post-necrotic hepatic cirrhosis.

Discussion

This trial was designed to assess the tumour-inhibitory effect of the joint administration of thiotepa and testosterone in breast cancer. Either drug will induce a regression of tumour growth (Adair, 1947; Bateman, 1955). The results reported here indicate that the simultaneous administration of both drugs enhances their individual effects. Thus objective improvement was obtained in 30 cases (88%) of the present series, whereas tumour regression may be expected in approximately only 33% of breast cancers treated with testosterone. Olson (1958), in his series of 10 cases of advanced breast cancer treated with thiotepa alone, obtained regression of tumour growth in three.

The response obtained in the 11 patients of this series treated with thiotepa alone was less satisfactory than in those receiving both drugs. The enhanced effect of using testosterone and thiotepa jointly may be due to some synergistic action between the two drugs, but it is more probably due to the much greater total dose of thiotepa that could be used in the patients receiving testosterone before marrow depression occurred (Table III). This impression is supported by Bateman's (1955) finding that marked tumour regression could be readily induced by injecting thiotepa direct into an accessible metastatic nodule. By this means she obtained very high local concentration of thiotepa with minimal toxic systemic effects. Murphy *et al.* (1958) have shown that the administration of thiotepa to the pregnant rat causes severe teratogenic effects on the foetus, whereas the absence of any deleterious effect on the foetus removed from Case 1 supports the contention that testosterone protects normal marrow and normal growing tissues against the depressive action of thiotepa.

The apparent ability of testosterone to increase marrow tolerance to thiotepa is of considerable interest. Investigations at present in progress appear to suggest that it is connected more with the androgenic effect than with the protein anabolic effect of the hormone. As it is possible to link the functional groups of an alkylating agent on to a wide variety of organic compounds it may be possible to synthesize an ethyleneimino compound of testosterone. Clinical trial of such a drug in breast cancer would be of great interest.

The clinical, histological, and radiological evidence of destruction of malignant cells obtained in the advanced cancers of this series suggests the possibility of completely eradicating a tumour and its metastases by chemotherapy. This question cannot be settled by treating only the advanced clinical case, as such a patient may have already passed the point of no return. The experimental work of Shapiro and Fugmann (1957) in the chemotherapy of breast cancer in mice is pertinent in this respect. They found an inverse relationship to exist between the therapeutic effect and the number of cancer cells. Case 2 illustrates a possible danger of chemotherapy in the late cancer. It is feasible that the rapid breakdown of cancer tissue induced by the chemotherapy, with the subsequent liberation of the products of necrosis, caused the liver damage and failure in this patient.

Considerations such as these, and for reasons already given in the introduction, finally induced us to abandon radiotherapy in favour of chemotherapy as an essential part of the primary treatment of early breast cancer. Seven patients have been so treated. Although we already have evidence of the effectiveness of the treatment from the histological studies of the tumours and the absolute regression of the axillary lymphadenopathy, proof of total eradication of their cancers may only be derived from progress studies over the succeeding years. Case 1, the pregnancy carcinoma, is of importance in this respect, as in this particular type of carcinoma the expectation of life is very short owing to its propensity to metastasis very early and widely (Willis, 1953). This patient was in excellent health, showing no evidence of metastases one year after her mastectomy.

A major difficulty was to decide when chemotherapy should be finally stopped. Thus, although apparent eradication of the growth with healing in skeletal and other metastases could be demonstrated comparatively easily, it must not be deduced that all the cancer cells are dead. It was for this reason that patients were put on a periodic maintenance dose of thiotepa. Again experience and time are required to decide whether the present maintenance dose is adequate. A difficulty in the future may arise from the emergence of a resistant strain of cancer cells in any one patient following the eradication of the susceptible cells by thiotepa. So far this has not arisen. It may be necessary in the future to use other antimitotic agents instead of or in combination with thiotepa. From clinical studies such as these undoubtedly better agents will be found and better techniques for use of the available agents will be elaborated. It is felt that at the present time a wider use of chemotherapy as an alternative to radiation should be made in breast cancer.

Summary

Thirty-four cases of breast cancer at various stages were treated with either thiotepa alone or thiotepa and testosterone. Marked tumour inhibitory effects were obtained in 30 patients. The most satisfactory results were obtained in the group receiving thiotepa and testosterone. Arising out of the results obtained with the advanced cancers, a trial of surgery and chemotherapy as opposed to surgery and radiation is advocated for early breast cancers, and the preliminary results with the first patients in such a trial are described.

Our thanks are due to Lederle Laboratories Division, Cyanamid of Great Britain Limited, for generous supplies of thiotepa.

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G. W. WATSON AND R. L. TURNER: BREAST CANCER

FIG. 1.—Metastasis in humerus before (left) and after (right) treatment.

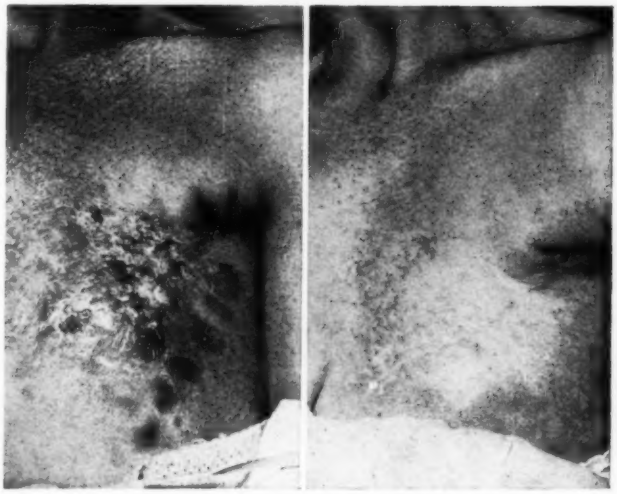

FIG. 2.—Ulcerated skin metastasis before (left) and after (right) treatment.

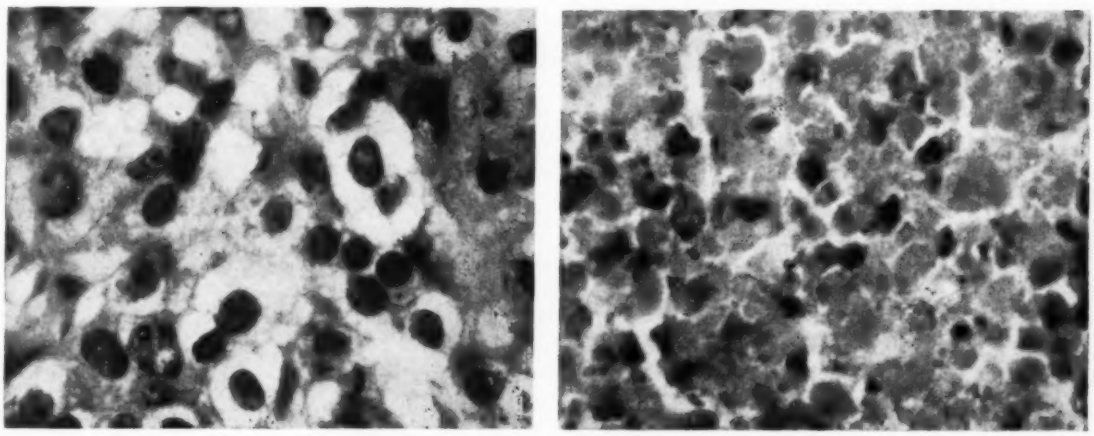

FIG. 3.—Early (left) and late (right) cytological effects of treatment.

P. M. PETERS: FROZEN-SECTION DIAGNOSIS

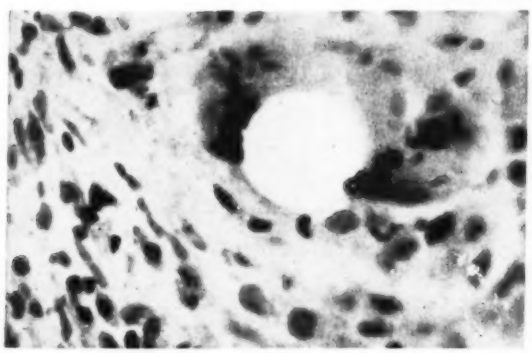

FIG. 1

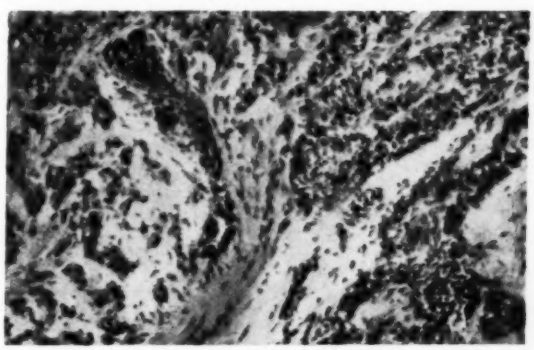

FIG. 2

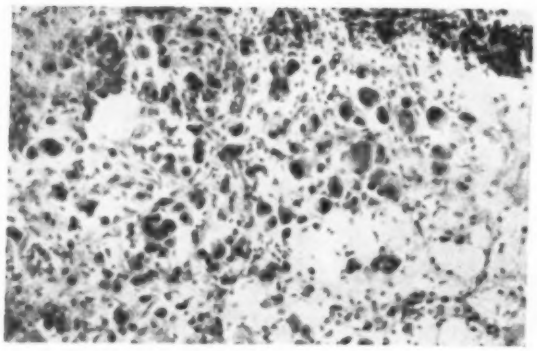

FIG. 3

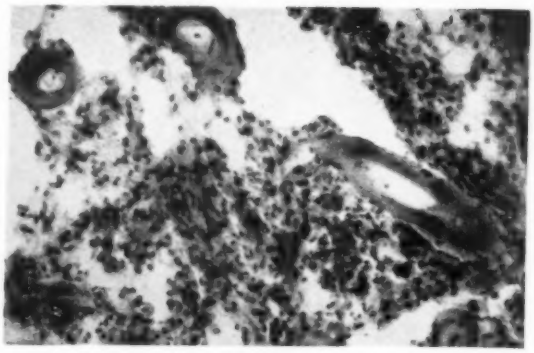

FIG. 4

FIG. 5

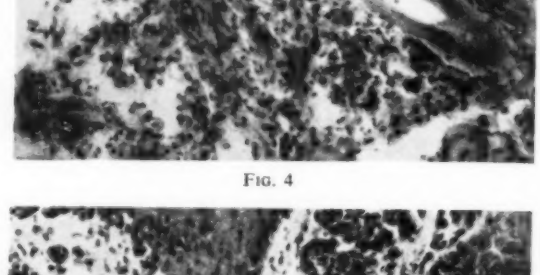

FIG. 6

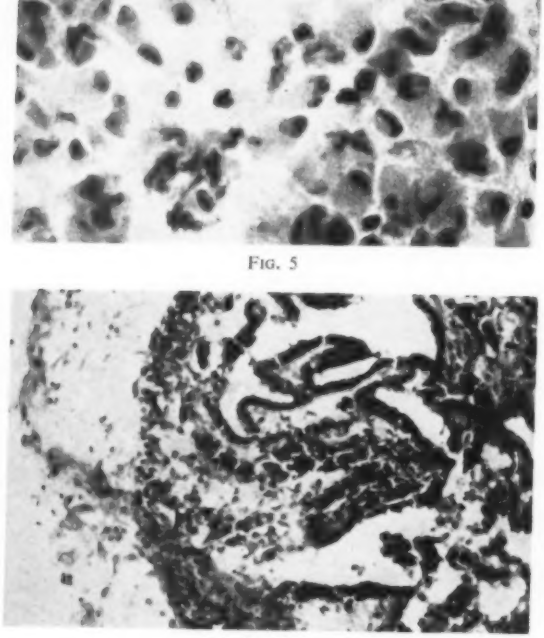

FIG. 7

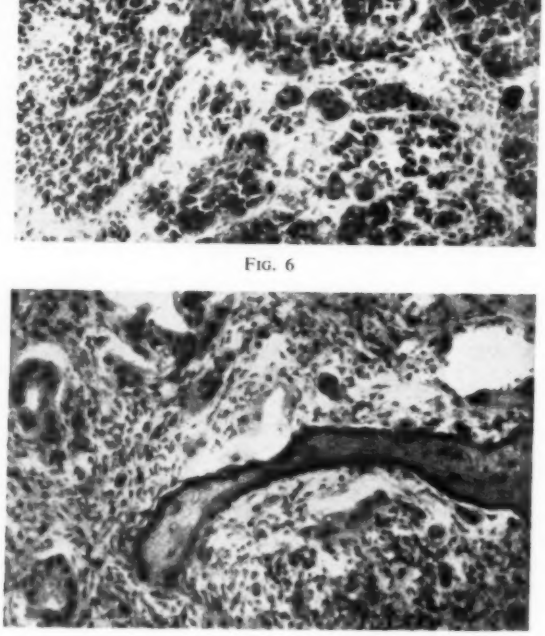

FIG. 8

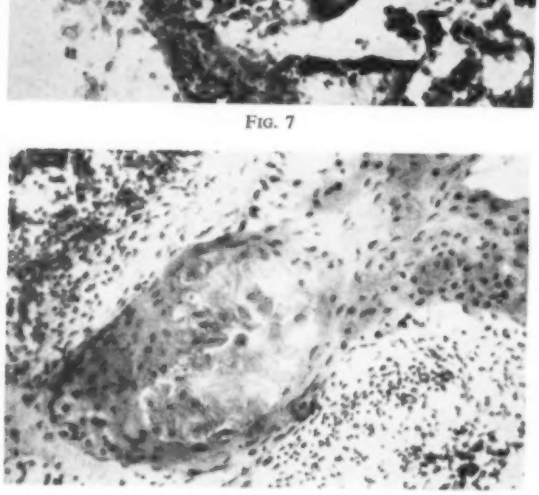

FIG. 9

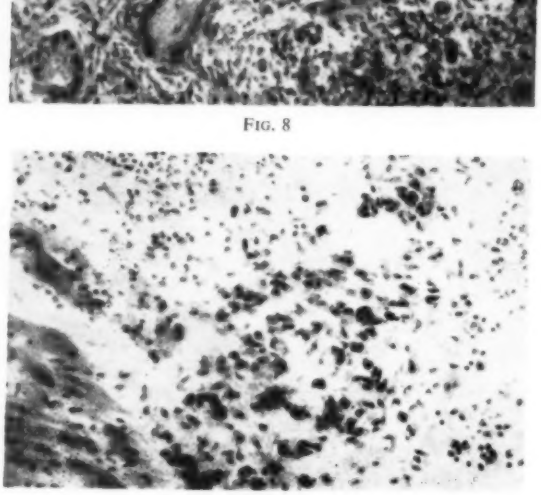

FIG. 10

FROZEN-SECTION DIAGNOSIS*

BY

P. M. PETERS, D.M.

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[WITH SPECIAL PLATE]

Rapid histological diagnosis by frozen section is a classical method that is not widely used in this country, although the demand would appear to be increasing. The late Dr. Ernest Shaw, of the Royal Northern Hospital, did pioneer work of the first importance in this field from the end of the last century onwards (see Shaw, 1910, 1923). Most of the literature, however, comes from the U.S.A. There the method has been generally favoured and was formally recommended by the American College of Surgeons (cited by Hellwig, 1935). Rather surprisingly, there have not been many analyses of results. The purpose of this paper is to attempt such an analysis, mainly from the point of view of validity of reporting and value, if any, to the surgeon.

Routine Method

The pathologist receives the biopsy specimen in the theatre and selects the block and surface to be cut. The section is cut from the fresh unfixed tissue by an expert technician, but the pathologist should be able to do this himself if necessary. The finished section is 5–10 μ thick, is stained by haematoxylin and eosin, is permanent, and takes from 7 to 10 minutes (per block) to prepare. A few special stains can be used—for example, for free iron—but are not often necessary. The quality of the routine frozen section may be judged by the accompanying low- and high-power photomicrographs (Special Plate, Figs. 1–10), all of which, except Fig. 10, are from cases of the present series. The use of the phase contrast microscope to plumb the depths of the section, as suggested by Fisher (1958), can be seen to be totally unnecessary. The apparatus for the frozen technique is easily transportable and the process can be done in any room close to the theatre; running water and electricity are advantages but are not indispensable.

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P. M. PETERS: FROZEN-SECTION DIAGNOSIS

FIG. 1.—Fat necrosis of breast. Foreign-body giant cell in focus of inflammatory cell infiltration and active fibrosis. Macroscopically this lesion closely simulated carcinoma. (H. and E. ×550.)

FIG. 2.—Carcinoma of breast. Common type. (H. and E. ×125.)

FIG. 3.—Large pleomorphic-celled carcinoma of breast invading fat. (H. and E. ×125.)

FIG. 4.—Meningioma with psammona bodies, incidentally demonstrating origin of such bodies from blood vessels. (H. and E. ×125.)

FIG. 5.—Cellular glioma. Area of gemistocytic astrocytes. (H. and E. ×550.)

FIG. 6.—Malignant melanoma of skin. (H. and E. ×125.)

FIG. 7.—Secondary adenocarcinoma in peritoneal fat. Macroscopically a miliary lesion on root of mesentery. (H. and E. ×125.)

FIG. 8.—Secondary adenocarcinoma in bone (vertebra). (H. and E. ×125.)

FIG. 9.—Secondary squamous-celled carcinoma in lymph node. (H. and E. ×125.)

FIG. 10.—Aschoff body in myocardium. Sudden death in infant. (H. and E. ×125 enlarged 1½.)

After the frozen section is reported verbally in the theatre, the tissue is processed by the paraffin method as a routine and the final written report is issued as follows:

Frozen section reported in theatre as .....
Specimen (macro.) .....
Histology (paraffin) .....

In every case, therefore, accurate comparison of the frozen and paraffin reports is available for both the surgeon and the pathologist.

Present Series

Material.—This consists of slides, blocks, and reports of 188 consecutive cases in which histological diagnosis by frozen section was given in the theatre (whole series). In 147 cases the clinical diagnosis and macroscopic tissue diagnosis were also recorded at the time (fully recorded series).

The work began in September, 1952, and continues; the last entry, however, to be included in the present analysed series is dated May 9, 1957. Thus the annual totals for comparison extend over four complete years: 1953 to 1956, the totals being 9, 18, 55, and 75 respectively.

This increase may be compared with the figures from the Presbyterian Hospital, New York, where there were 28 frozen sections in 1929 and 923 in 1954, the operations with specimens for these two years totalling 2,066 and 6,511 respectively (Stout, 1956).

Whole Series (188 Cases) Validity of Reporting

In 175 cases (93.1%) the frozen and the paraffin reports have been identical. In 7 cases (3.7%) there has been an unimportant difference between the two reports. In 6 cases (3.2%) the frozen report has been wrong; in one of these the diagnosis was given in the theatre as essentially uncertain and the various possibilities were mentioned. The subsequent paraffin sections of this case were so difficult that they were referred to the consultant panel in morbid histology, who gave only a majority opinion. For the purposes of this analysis this case and the unimportant difference group may reasonably be added to the first group to represent working or practical validity. These figures are shown in Table I for comparison.

TABLE I.—*Frozen-section Validity Compared with Paraffin*

	Frozen and Paraffin identical or similar	Unimportant Difference	Frozen Wrong
Absolute validity ..	175 (93·1%)	7 (3·7%)	6 (3·2%)
Working	183 (97·3%)	—	5 (2·66%)

The wrong group of five cases is further broken down in Table II and compared with Sjölin's (1955) results in a much larger series of frozen sections (1,467 blocks: 504 patients).

TABLE II.—*Error Analysis*

Total	5 (2·66%)	(Sjölin, 3·2%)
Faulty sampling by pathologist ..	3 (1·6%)	(,, 2·5%)
Histological misinterpretation	2 (1·06%)	(,, 0·7%)

The two misinterpreted cases were: (1) atypical duct papilloma of breast, doubtful malignancy (paraffin); frozen section reported as early carcinoma (false positive); and (2) carcinoma of thyroid (paraffin); frozen section reported as benign (false negative). The surgeon remained sufficiently suspicious of this lesion, however, to operate as for carcinoma.

It should be noted that sampling errors also occur in paraffin work, as the experienced histologist

recognizes by taking deeper cuts in the block or selecting more tissue when a negative surprise turns up in a section.

When it is remembered that most cases are selected for their diagnostic difficulty, it is safe to assume that the correspondence between frozen and paraffin reporting is high enough for the method to be used with confidence.

Sampling errors by the surgeon have not been included, as irrelevant to an analysis of validity of reporting; in practice they have been very infrequent.

There are very few normal or pathological tissues which are quite unsuitable for the method, though some are technically more difficult than others. Even tissue containing light spicules of bone can be cut (Special Plate, Fig. 8). Excellent preparations can be made from post-mortem tissues if fresh, and a frozen section may be very useful on occasion, particularly in a forensic case. For example, a 3-year-old infant died suddenly and unexpectedly, the only history being of rather vague joint pains. Gross changes at necropsy suggested rheumatic carditis, but were not definite. Frozen section of myocardium showed a typical Aschoff body (Special Plate, Fig. 10), and it was therefore possible to give an immediate explanation to the coroner and so to the bereaved parents. Special studies of frozen-section work on particular tissues have been made by some workers. They include prostate (Culp and McDonald, 1954), stomach (Jones and Bullock, 1954), skin (Mescon *et al.*, 1951), joints (Swift, 1936), and a recent analysis of breast lesions (Sandison, 1958). The type of tissue or anatomical site of the present material is given in Table III.

TABLE III.—*Tissue and Organs Examined in 188 Cases*

Breast	122	Ovary, uterus, and vagina	3
C.N.S.	17	Testis	3
Skin and subcutis	16	Stomach	2
Thyroid	6	Rectum	2
Lymph nodes	5	Bronchus	2
Peritoneum	4	Urinary bladder	1
Bone and joint	4	Parathyroid	1

Fully Recorded Series (147 Cases)

It would appear from Table IV that in 22.4% of 147 cases the frozen section was of some direct use (cf. Dockerty's (1952) estimate of approximately 20%). Apart from straight pathological diagnosis, this group includes special information such as limits of spread of a malignant tumour and tissue identification—for example, testicular tissue in a ? hermaphrodite ? cryptorchid.

TABLE IV.—*Macroscopic Tissue Diagnosis Compared with Frozen-section Diagnosis*

	Cases
Macro. and frozen the same	112 (76·2%)
,, doubtful or wrong, frozen diagnostic	33 (22·4%)
,, right, frozen wrong	2 (1·3%)

Some value in the fact of confirmation may be claimed for 76.2% of the group. It may, for example, be helpful with a very anxious patient or relative.

Brief Notes of Selected Cases

1. 1004/54. Lump in breast. Frozen section typical fibroadenoma with a small contiguous and partly enveloping carcinoma; very difficult combination to detect macroscopically.

2. 2522/55. Pigmented skin tumour, macroscopically ? malignant melanoma, ? sclerosing angioma. Frozen section, cellular tumour loaded with pigment. Iron stain on frozen section showed massive deposits of haemosiderin, distribution approximately similar to that in the H. and E. Diagnosis of sclerosing angioma given, confirmed in the paraffin section.

3. 885/46. ? diffuse carcinoma in lactating breast, the macroscopic appearances of the tissue at exploration tending to support this diagnosis. On frozen-section report of very inflamed lactating breast, a deeper incision was made into the mass and a large "artesian well" of an abscess found and drained.

4. 1495/56. Doubtful mass in breast. Macroscopic appearances very difficult to interpret. Frozen section—anaplastic carcinoma 1 cm. diameter, surrounded by zone of inflamed and degenerate breast tissue. Secondaries found in axillary lymph nodes in main specimen.

5. 1758/56. Needle biopsies for ? cerebral tumour. One of the biopsies showed inflamed degenerate brain tissue, as in the vicinity of a tumour. This indicated another burr-hole in a definite direction, and the biopsy through this contained a particle of astrocytoma (Special Plate, Fig. 5).

6. 1977/56. Intracranial tumour, clinically and radiologically; ? suprasellar meningioma, ? craniopharyngioma. Sella turcica normal. At operation the tumour was found to be a spherical dark-red mass which suggested the additional possibility of aneurysm. Frozen section of a needle biopsy showed chromophobe pituitary adenoma. In view of the radiologically normal sella the surgeon was rightly sceptical, but further dissection showed the broad pedicle of the tumour largely replacing the diaphragma sellae, and the growth was removed. Clearly the tumour had arisen very superficially in the pituitary and had grown straight up and out of the fossa.

7. 2584/56. Pigmented tumour of skin; ? angioma, ? malignant melanoma. Macroscopically the cut surface appeared solid and black, and minute streaks of pigment were visible, streaming away through the subcutis at the base and margins. There was no doubt in the minds of all those in the theatre that this was a malignant melanoma. Frozen section showed a cavernous haemangioma welded into a solid mass by gross recent and old haemorrhage, the streaking visible at the base being phagocyted haemosiderin.

8. 2604/56. A girl of 19 with a tumour in the pituitary region; ? craniopharyngioma, ? pituitary adenoma. At operation the tumour was seen as a dark-red conical mass occupying the sella turcica and projecting straight upward. Frozen section reported as diagnosis uncertain; ? atypical pituitary adenoma, ? angio-endothelioma. The tumour was removed and the paraffin sections were equally difficult to interpret. The blocks were referred to the consultant panel in morbid histology (see above), and by a majority opinion the diagnosis was given as chemodectoma. Local recurrence about six months later, with clinical evidence of invasion of the cavernous sinus. Some improvement followed radiotherapy.

9. 825/56. Small lump in breast, clinically and macroscopically probably carcinoma. Frozen section—focal fat necrosis (Special Plate, Fig. 1).

Other Rapid Methods

Cytological methods are sometimes used on organized tissue by scrape, smear, or wet impress techniques. Personally I have found these methods inferior to the frozen section. Tumour diagnosis and classification is and will remain histological; that is to say that architecture, micro-anatomical relationships, and assessment of the biological property of invasiveness carry as much or more weight than cytological detail. If, therefore, a histological preparation is possible, it seems clearly wrong to use a method that disrupts these aspects of a lesion; and one that may have as much or more artifactual disadvantage (thick smears, distortion, and bursting of cells), and, if the specimen be small, may leave no material for paraffin histology. It is perhaps not widely appreciated that a specimen as unpromising as a needle biopsy of pathologically softened brain measuring 2 by 1 mm. can be adequately sectioned (fresh) by the frozen method and still leave

something to process at leisure. Without bearing in any way on the value of exfoliative or smear cytology in general, it is my view that, if a macroscopic piece of true organized tissue, however small, is available, the frozen section should have pride of place in the immediate diagnosis of tumours or other lesions (see also Carleton and Drury, 1957), although supplementary information on cell detail may be given by cytological methods (cf. Bamforth and Osborn, 1958).

Terry's method (Terry, 1928, 1929; Hellwig, 1935) consists in cutting a thin slice of tissue by razor, free-hand staining with neutralized polychrome methylene blue on one surface only, and relying on translucency to reveal a recognizable picture. In my view, again, it has only speed and ingenuity to recommend it; the preparations are inevitably far below the standard required for critical diagnosis.

Conclusions

Immediate histological diagnosis by frozen section is an old-established method of considerable value in surgically doubtful lesions. A good permanent haematoxylin-and-eosin-stained section 5–10 μ thick can be produced in from 7 to 10 minutes. In the present series of 188 consecutive cases reported in the theatre, the working validity of reporting as compared with the subsequent paraffin section has been about 97%. In five cases (2.7%) wrong diagnoses were made; of these, three (1.6%) were due to faulty sampling by the pathologist and only two (1.06%) were histologically misinterpreted. In addition there was one case in which the diagnosis was uncertain and the paraffin sections were equally baffling.

From full data recorded in 147 cases at the time, the information given to the surgeon has been of some direct use in one way or another in about 22% of cases. In about 76% of cases the frozen section may be said to have had confirmatory value.

The traditional criticisms of the method have not therefore been supported by the present analysis. These are that: (1) if the tissue diagnosis is difficult for the surgeon it will be as difficult for the microscopist; and (2) the risks in reporting in a hurry on an imperfect section are too high.

On the contrary, by settling the diagnosis in doubtful cases at the first operation, (1) the risk of metastasis is diminished, (2) the patient is spared the anxiety of waiting for a paraffin biopsy report, (3) the patient has one anaesthetic only, (4) the rare unnecessary radical operation is prevented, and (5) in brain tumour cases the amount of needling is reduced to a minimum and unnecessary craniotomy may be avoided in rapidly declining patients.

Few tissues, normal or pathological, are unsuitable for the method, and tiny fragments—for example, needle biopsies—can be reported on and still leave a residue for paraffin confirmation. Even tissue containing spicules of bone can be cut (Special Plate, Fig. 8). Where a piece of organized tissue could be produced, the method was found to be superior to other rapid methods of diagnosis.

In Dr. Shaw's days the time taken by the method was counted something of a disadvantage, but this is not so with modern anaesthesia. To-day, the average of 7 to 10 minutes required to produce a permanent section of good quality stained in the way that the pathologist sees daily adds nothing to the patient's risk.

Naturally, if the tissue diagnosis is obvious macroscopically, the surgeon will proceed straight away; it may, however, still be worth cutting a frozen section to give the grade of a tumour or to define the limits of spread.

Summary

The classical method of rapid histological diagnosis by frozen section of tissue from the theatre is reviewed and the data from 188 cases are analysed.

The method is found to be reliable, and useful in selected cases.

It is a pleasure to record my indebtedness to Mr. Hayward Cox, A.I.M.L.T., who cut the sections, took the photomicrographs, and also read the manuscript. I thank Dr. M. Hynes, Mr. R. S. Murley, Mr. L. C. Oliver, and Mr. A. Small for reading the draft and for many valuable suggestions; and Dr. H. Caplan, who, in addition to this, reported five of the cases. My thanks are due to Sir Bentley Purchase for permission to include one case. I am obliged to Mrs. H. M. Page for secretarial help.

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THE CYANOTIC (SYNCOPAL) ATTACK IN FALLOT'S TETRALOGY

BY

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Patients with Fallot's tetralogy are prone to attacks of increased cyanosis, with associated loss of consciousness ("cyanotic or syncopal attacks"; "anoxic spells"). These patients may recover spontaneously from the attacks, but fatalities are known to occur. A history of syncopal attacks makes corrective surgery, or if this is not feasible systemic-pulmonary arterial anastomosis, an urgent necessity.

The mechanism of the attack was not definitely known until recently. Wood (1958) has shown that it may be precipitated by increased obstruction to the flow of blood through the right ventricular outflow tract into the pulmonary artery, with increased shunting of deoxygenated blood into the aorta.

We have recently had the opportunity of studying a cyanotic attack occurring during the course of cardiac catheterization. The mechanism of production of the attack as described by Wood was confirmed. The problem of management of the attack gave rise to anxiety, and several forms of therapy were tried, with varying success.

Case Report

A girl aged 2¼ years was referred for diagnosis of her congenital heart condition. She was the product of a normal pregnancy and labour. For the first three days of life she was blue, but the cause of this was not determined. She remained well until 9 months of age, when she started to exhibit blueness of the lips and of the circumoral region on walking. She experienced shortness of breath on exertion and would rest after walking 10 yards. She did not squat. She had had one attack of rapid breathing with intense cyanosis and unconsciousness lasting 20 to 30 seconds while sitting.

Examination revealed a well-nourished, well-developed girl: height 36 in. (91 cm.); weight 30 lb. (13.6 kg.). There was no clinical cyanosis and the fingers were not clubbed. Blood pressure in the right arm was 90/50 mm. Hg, and in the right leg 120/80 mm. Hg. The jugular venous pressure was not raised, and there was no hepatomegaly or periorbital oedema. A systolic thrill was palpable in the third left intercostal space, and a systolic thrust and diastolic shock were present in the second left intercostal space. The first heart sound was normal. The second heart sound was single, but in some cycles a very soft second component was audible, and the "splitting" was wider than normal. A grade 4 ejection systolic murmur was present along the left sternal edge, loudest in the third left intercostal space.

Electrocardiography showed marked right ventricular hypertrophy. Radiological examination of the chest revealed a cardiothoracic ratio of 58%, with enlargement of the right atrium and right ventricle, and prominence of the ascending aorta and the aortic knuckle. The main pulmonary artery was normal, but the lung vascularity was diminished.

Phonocardiography confirmed the auscultatory findings and clearly demonstrated a soft second (pulmonic) component of the second sound, 0.06 to 0.08 second after the first component. The systolic murmur continued to just beyond the first (aortic) component of the second sound.

The clinical diagnosis was "Fallot's tetralogy (acyanotic)."

Cardiac catheterization was carried out to confirm the diagnosis. The child received premedication consisting of pethidine 30 mg., "stemetil" 30 mg., and nalorphine hydrobromide ("lethidrone") 1.5 mg. by intramuscular injection. During the procedure she was given small quantities of "nereval" intravenously (Dr. K. Jooste). A No. 6 Cournand catheter was introduced via a left brachial vein through the right heart chambers into the left pulmonary artery. Pressure measurements and blood samples were taken on withdrawal of the catheter. When the catheter was in the pulmonary outflow tract the electromanometer failed, and while another was being obtained the catheter was left *in situ*. After about 20 minutes the child became hyperpnoeic, markedly cyanosed, and deeply unconscious. Her pupils were pin-point in size. Tendon reflexes were extremely brisk and equal, with ankle and knee clonus and extensor plantar responses. The systemic blood pressure was 90/50 mm. Hg (its pre-catheter level) and her radial pulses were bounding at a rate of 170 a minute. The precordial systolic murmur was barely audible. Electrocardiography showed the tachycardia to be sinus in origin. She was given further intravenous "nereval" with diminution of the hyperpnoea, abolition of the extensor plantar responses and of the clonus, but no other significant changes. The diagnostic study was completed as rapidly as possible.

The findings at cardiac catheterization (see Table) indicated a severe infundibular pulmonic stenosis with approximately equal pressures in right ventricle and brachial artery, and marked arterial desaturation. These findings were suggestive of Fallot's tetralogy. The condition of the patient precluded more detailed study.

The cyanotic attack persisted after catheterization, despite continuous oxygen administration, and about two and a half hours after the beginning of the attack the child was still cyanosed and deeply unconscious, with "pin-point" pupils. At this stage, quite empirically, she was given 6 ml. of 2% procaine hydrochloride intravenously, and within seconds she sat up and asked for water. The systemic blood pressure remained at 90/50 mm. Hg and the pulse rate at 170. The systolic murmur was much louder. A few minutes later she relapsed into coma again; she was given a second injection of the same dose of procaine hydrochloride, with an equally dramatic effect, but once more she relapsed into deep coma.

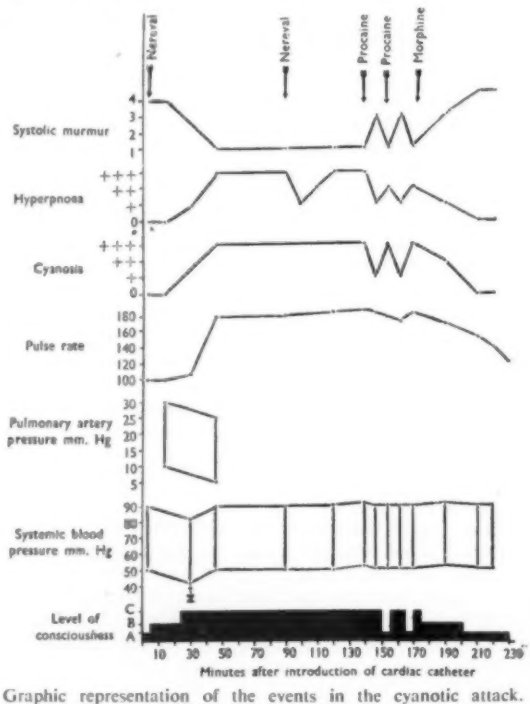
Findings at Cardiac Catheterization

Site	Pressure (mm. Hg)			O_2 Saturation %
	Systolic	Diastolic	Mean	
Left pulm. artery*				70·5
Main pulm. artery { 1* ..	30	10		70·5
Main pulm. artery { 2 ..	25	5		41·0
Right ventricle (outflow tract)	28	0–5		
,, ,, body ..	88	0–5		42·5
Brachial artery	85	40		52·5
Right atrium			6	

* Before cyanotic attack.

She was then given morphine sulphate ¼ gr. (8 mg.) intramuscularly, and over the next 10 to 15 minutes cyanosis lessened considerably, and she was in a sleep from which she could be roused. Her pupils enlarged somewhat, and reacted to light. The murmur was now again grade 4, and the pulse rate gradually slowed to 120. Over the next few hours she "slept off" the effects of the morphine, and returned to her "pre-catheter state." Throughout the day the systemic blood pressure remained unchanged.

The events of this cyanotic attack are shown graphically in the Chart.



Graphic representation of the events in the cyanotic attack. O = Absent. + = Mild. ++ = Moderate. +++ = Severe. A = Conscious. B = Unconscious, but responds to painful stimuli. C = Unconscious and unresponsive to painful stimuli. Z = Direct intra-arterial measurement.

Discussion

The sudden increase of cyanosis, with diminished intensity of the systolic murmur, was probably

precipitated in this case by the prolonged presence of a cardiac catheter in the pulmonary outflow tract. The diminution of the intensity of the systolic murmur indicated diminished flow across the pulmonary valve, but that this was not due to decreased systemic arterial resistance is shown by the sustained systemic blood pressure. Tachycardia was not responsible for the changes, as the heart rate remained rapid for some time after the disappearance of cyanosis and the return of a loud systolic murmur.

Thus the findings in this case confirm Wood's (1958) hypothesis that the cyanotic attack is precipitated by temporarily increased obstruction at the pulmonary outflow tract, with greatly increased shunting of blood from right ventricle into aorta. Unlike Wood's cases, our patient showed only a slight drop in pulmonary artery pressure during the attack with no change in the pulse pressure, and deep coma was present with an arterial oxygen saturation of 52.5% (Wood states that coma ensues when the arterial oxygen saturation falls to about 20%).

It would seem that the level of arterial desaturation at which the patient loses consciousness is, at least partly, dependent on the resting level of saturation, which in this patient was presumably normal or almost normal, in view of the absence of clinical cyanosis. The fact that the pulmonary artery pressure diminished only slightly might suggest that the obstruction to the pulmonary flow in our patient was less marked than in Wood's cases. It is significant, however, that the pulmonary artery pressure did not rise, which one would have expected were the obstruction to pulmonary flow produced by an increased pulmonary arterial resistance.

The findings in this case indicate that the dangerous cyanotic attack may occur in those patients with Fallot's tetralogy with no clinical cyanosis, a finding which we have observed in other such cases (to be published).

When faced with a cyanotic attack the practitioner may use procaine intravenously as an emergency measure, but for a sustained effect morphine would appear to be more suitable. It must be mentioned, however, that we have had patients in whom morphine has failed to stop the attack. Other narcotics might presumably be efficacious, and Wood has recommended cyclopropane anaesthesia. It must be stressed that oxygen administration is not, by itself, effective therapy.

Summary

A patient with "acyanotic Fallot's tetralogy" developed a cyanotic (syncopal) attack during cardiac catheterization. The attack was probably precipitated by the prolonged presence of the catheter in the pulmonary outflow tract. The condition was studied haemodynamically, and it was believed that the attack was due to increased resistance to the flow of blood through the narrowed infundibulum. The treatment of the attack was difficult, and procaine intravenously was found to be effective, although the effect was not sustained. Morphine proved effective in relieving the attack.

We thank Drs. M. J. Meyer, W. Scott, and K. Jooste for their assistance during the cardiac catheterization. Dr. B. Senior suggested the use of procaine intravenously, and we are grateful to him for this advice.

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CASE OF LATENT NEPHRITIS TREATED WITH PREDNISOLONE

BY

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It is now accepted that the nephrotic syndrome is often amenable to treatment with steroids and corticotrophin (Arneil and Wilson, 1952; Arneil, 1956). The newer steroid preparations, especially prednisolone, seem to be particularly useful, and cases of nephrosis have been reported to respond to prednisolone after failure to respond to cortisone and prednisone (Holland *et al.*, 1958).

Cortisone and corticotrophin have also been used to treat acute and latent nephritis (Thorn *et al.*, 1950; Burnett *et al.*, 1950), but the results have generally been disappointing. Some workers (Michaels and Walters, 1953) found an increase of haematuria during treatment, and Philpott and Briggs (1953) concluded that cortisone and corticotrophin were valueless in the treatment or prevention of subacute nephritis complicating the Schönlein–Henoch syndrome.

A case of acute nephritis occurred in a general practice, and it became evident that the disease was progressing into a latent phase with persistent albuminuria, haematuria, and cast formation. I decided to observe the effect of prednisolone treatment.

Case Report

A boy aged 16 was referred to me in March, 1957, albuminuria having been detected at a medical examination held for prospective employees of the urban district council. About two weeks before this examination he had complained of a sore throat and his temperature was said to have been over 100° F. (37.8° C.) for two days. His throat symptoms resolved in a few days, but he then noticed slight backache.

On examination there was slight facial oedema but no ankle oedema; the blood pressure was 145/95. The urine was reported to contain albumin ++, red blood cells +++, and cellular and granular casts ++. The blood urea was 38 mg./100 ml.

A diagnosis of acute nephritis was made, and the patient was confined to bed and given a low-protein diet. After 12 weeks of absolute bed rest there was no improvement.

On June 8, 1957, he was transferred to a hospital, where the regime of bed rest and low-protein and low-salt diet was continued. He was discharged on October 1, still excreting red cells, casts, and albumin, but the blood pressure had fallen to 125/80. He was sent for two weeks' convalescence.

He returned home on October 16 and was then having a normal diet. Two days later he developed gross haematuria, the urine being the colour of port wine, albumin ++++; blood pressure 135/80. There was no oedema. His temperature was 99° F. (37.2° C.). Bed rest was again enforced.

On October 21 his temperature was normal, E.S.R. (Westergren) 32 mm./hour, blood pressure 130/80. The urine was slightly "smoky" to the naked eye. There was gross microscopic haematuria, and granular and cellular casts were abundant. The blood urea was 38 mg./100 ml. During the day he complained of toothache, and on closer questioning admitted having had intermittent pain several times before.

By October 31 the E.S.R. had fallen to 5 mm./hour, blood pressure 120/80, temperature normal. His general condition was satisfactory apart from the persistence of

albumin (1 g./litre), red cells, and cellular casts in the urine. The blood urea, serum proteins, and serum cholesterol were normal.

During the first week in November he developed a dental abscess; culture showed the organism to be an alpha-haemolytic streptococcus sensitive to penicillin. A 10-day course of crystalline penicillin, 0.5 mega unit twice daily, was started on November 14 and the next day the carious tooth was extracted under general anaesthesia. There was no improvement following this procedure; the clinical and laboratory findings remained unchanged.

On November 30 he developed an *Escherichia coli* urinary infection. The organism proved to be sensitive to sulphanilamide, streptomycin, and chloramphenicol. The infection responded to a six-day course of sulphadimidine, 2 g. every six hours. The excretion of albumin, red cells, and cellular casts persisted as before.

Investigations

Twelve days before starting steroid therapy the following routine was established. All fluid taken was carefully measured and recorded, the urinary output for each 24-hour period being similarly recorded and the albumin content estimated by the Esbach method. The urea clearance test was normal, and after 24 hours of fluid deprivation the urine specific gravity was 1030. The blood pressure was recorded daily. A Mantoux jelly test was negative. Weekly estimations of the serum electrolytes and bicarbonate reserve were carried out. The E.S.R., serum proteins, haemoglobin, blood urea, and urinalysis were determined weekly as before.

Paper electrophoresis of the serum and urinary proteins was carried out on three occasions: firstly, during treatment on January 3, 1958; secondly, four weeks after treatment, on February 25; and, finally, 34 weeks after treatment, on August 8. A modification of the method described by Flynn and Mayo (1951) was used and bromocresol-green was chosen as the protein dye. Readings were made by a photoelectric scanner. The urinary electrolytes were removed by an ion-exchange resin ("amberlite" monobed resin MB—1). The solution was then freeze-dried *in vacuo* at −4° C. and the proteins were redissolved.

The patient was given a high-protein (126 g. a day), low-salt diet; the total salt intake did not exceed 2 g. a day.

Treatment

Prednisolone was started on December 16, 1957: 60 mg. daily for 10 days, then 40 mg. daily for 10 days, followed by 20 mg. for 10 days, and finally 10 mg. for 10 days. While he was receiving hormone treatment oral benzathine penicillin, 1 mega unit daily, was administered together with 1.5 g. of potassium chloride a day as the serum potassium was only 3.5 mEq/l. before treatment.

Results

Throughout treatment the blood pressure remained at 125/80; the E.S.R., blood urea, and haemoglobin remained normal. There was no evidence of sodium retention; indeed, the salt intake was increased after three weeks' treatment as the serum sodium had fallen from 138 to 120 mEq/l. The serum potassium remained at 3.5 mEq/l. in spite of the potassium chloride, but rose to 4.5 mEq/l. when the oral dose was increased to 2 g. a day. While on steroid treatment the serum cholesterol rose from 195 to 260 mg./100 ml., falling again to 180 mg./100 ml. after cessation of treatment.

Little effect on the albuminuria was observed, 1 to 2 g. of albumin being excreted in the urine a day: occasionally this value was exceeded and sometimes it was less than 1 g. a day. Seven months after treatment the albumin excretion averaged 1 g. a day.

On the fourth day of treatment the number of red cells in the centrifuged urinary deposit was reported as + (previously +++), and no casts were seen. At the end of the course the urine was either reported as free from red cells or "an occasional red cell seen" in the centrifuged deposit. Casts were always reported absent. No red cells or casts have been demonstrated in repeated samples during the seven months period following treatment.

The patient complained of epigastric pain on three occasions while receiving the larger doses of prednisolone. These attacks lasted one to ten minutes. They were not associated with nausea or vomiting and no abdominal tenderness was elicited.

The serum and urinary protein electrophoretic patterns are shown in Figs. 1–6, and the quantitative values are given in the Table.

Results of Electrophoresis of Serum and Urinary Proteins, Together with Some Biochemical Findings, and the Results of Microscopical Examination of the Centrifuged Urinary Deposit

	Jan. 3, 1958	Feb. 25	Aug. 28
Serum proteins (g. 100 ml.):			
Total	8	8·2	7·0
Albumin	3·52 (44%)	4·51 (55%)	3·64 (52%)
Globulin α_1	0·4 (5%)	0·57 (7%)	0·28 (4%)
" α_2	1·76 (22%)	1·23 (15%)	0·86 (12%)
" β	1·28 (16%)	0·82 (10%)	0·96 (14%)
" γ	1·04 (13%)	1·07 (13%)	1·26 (18%)
Urinary proteins (g./100 ml.):			
Total	0·14	0·43	0·1
Albumin	0·062 (44%)	0·38 (87·5%)	0·085 (85%)
Globulin α_2	0·046 (33%)	—	0·003 (3%)
" β	0·032 (23%)	0·04 (10%)	0·012 (12%)
" γ	—	0·01 (2·5%)	—
Blood urea (mg. 100 ml.)	39	24	37
Serum cholesterol (mg. 100 ml.)	260*	220	160
E.S.R. (mm./hour)	2	2	1
Urine:			
R.B.C.	Nil	Nil	Nil
Casts	"	"	"

* Estimated on January 21.

At the time of writing the boy was working as a labourer, and, apart from slight proteinuria, all clinical and biochemical examinations have failed to reveal any abnormality.

Discussion

Rennie (1958) defines latent nephritis as the persistence of albumin, blood, and casts in the urine six months after acute nephritis. Spontaneous recovery is possible, and 82% of those who recover do so within the first two years (Addis, 1948).

From a study of the electrophoretic patterns (Figs. 1 and 2) it will be seen that the serum shows a significant rise in the α_2-globulin. There is a slight fall of albumin

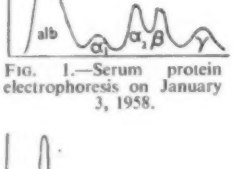

FIG. 1.—Serum protein electrophoresis on January 3, 1958.

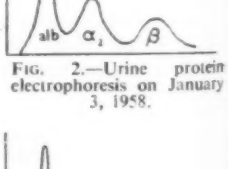

FIG. 2.—Urine protein electrophoresis on January 3, 1958.

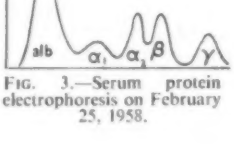

FIG. 3.—Serum protein electrophoresis on February 25, 1958.

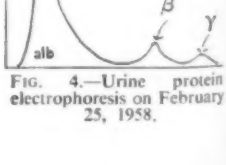

FIG. 4.—Urine protein electrophoresis on February 25, 1958.

and γ-globulin. Analysis of the urine shows that less than one-half of the total protein content consists of albumin and that one-third is made up of α_2-globulin. Squire (1953) gives a figure of 300,000 for the molecular weight of α_2-globulin compared with 69,000, the molecular weight of albumin. The leakage of the large globulin molecule indicates loss of selective permeability and therefore gross damage to the glomerular membrane (Hardwicke and Squire, 1955).

Two months after steroid therapy it is apparent that the serum proteins show a slight rise of the albumin fraction (Fig. 3). The general pattern is, however, unchanged. The urine picture is markedly different (Fig. 4). Only 12.5% of the total protein is globulin: the rest consists of albumin. This could be interpreted as a recovery of the selective permeability of the glomerular membrane.

The third analysis, made seven months after treatment, supports this view. The serum proteins (Fig. 5) are almost within normal limits, apart from a rather high α_2-globulin. The bulk of the urinary protein again consists of albumin; only 15% is made up of globulin (Fig. 6).

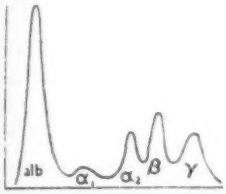

FIG. 5.—Serum protein electrophoresis on August 28, 1958.

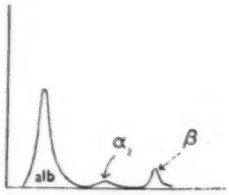

FIG. 6.—Urine protein electrophoresis on August 28, 1958.

Too much emphasis cannot be laid on the absolute values of the individual protein fractions estimated by paper electrophoresis (Wolstenholme and Millar, 1956). Furthermore, it is conceivable that some denaturation of the urinary proteins may occur as a result of the extraction methods. Only marked changes in pattern are therefore considered significant.

The fact that both red cells and casts were present in the urine for a period of nine months prior to treatment, but were suddenly reduced, and finally disappeared during and after treatment, suggests that the improvement was directly due to the hormone.

It would be tempting to suppose that prednisolone treatment had prevented the stage of latent nephritis from progressing into the chronic phase, and that the albuminuria was a legacy of permanent renal damage. Such an optimistic view is difficult to entertain on the result of one case, and past experience has shown that steroids rarely succeed in curing pathological processes. If it could be shown, however, that treatment prolonged the transition into the chronic phase then it would be worth while. Latent nephritis may smoulder for many years with little apparent deterioration in the patient's general condition, so the results of any form of treatment would be difficult to assess. Nevertheless, at the present time there is no known treatment which will directly influence the course of the disease, and it does seem that a trial of the newer synthetic steroid preparations would be justified.

Summary

In a patient with latent nephritis blood and casts disappeared from the urine during treatment with prednisolone. Evidence is given to suggest that the drug had a direct effect on the improvement of glomerular permeability.

It is considered that more extensive trials would be justified.

I thank Dr. D. G. Bennett for permission to publish this account and for his encouragement; Dr. J. Gibson and the staff of the Bath Central Laboratory for the biochemical investigations; and Messrs. Pfizer Ltd., who provided a generous supply of "delta-cortril" (prednisolone).

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SPONTANEOUS HAEMARTHROSIS IN OSTEOARTHRITIS OF KNEE

A REPORT OF FIVE CASES

BY

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Haemarthrosis of any joint, if associated with trauma, is usually coupled with a severe intra-articular injury. Spontaneous bleeding occurs in cases of blood dyscrasia, and sometimes will result from tumour invasion. It is known that small intra-articular haemorrhages occur in arthritic knees from time to time, often as the result of minor strain (DePalma, 1954); but it is not widely appreciated that these haemorrhages may be very extensive. Within the past two years I have been able to collect the details of five cases of spontaneous haemarthrosis of the knee. The history has been so characteristic that in two of the cases a firm diagnosis was possible before it was confirmed by aspiration. Although a "doughy" consistency is sometimes thought to be characteristic of a haemarthrosis, difficulty often arises in distinguishing it from an acute effusion. It is felt that the condition may often go undiagnosed and that, if recognized, early aspiration might reduce the period of disability.

Case Reports

Case 1.—A married woman aged 64 was admitted to hospital with a history of sudden swelling of the left knee while she was standing. She stated that three weeks previously there had been a similar incident. The second attack was described "as if the muscles tightened into a knot and the knee swelled." On the first occasion she

noticed that there was some bluish discoloration around the joint. On examination the knee was found to be tensely swollen and warm, the synovia having a "doughy" feeling. The leg was held with the knee slightly flexed, and any attempt to move it was acutely painful. Radiographs showed marked arthritic change around the patella with a vertical fissure through the bone. The knee was aspirated and 53 ml. of unclotted blood was removed. All investigations for blood abnormality or tumour proved negative. The lower limb was immobilized on a Thomas splint for two weeks and then mobilized. After two months the patient had regained a full range of movement.

Case 2.—A married woman aged 65 was seen as an out-patient with a history of sudden severe pain in the right knee when rising from a chair. Within a few moments the joint had become swollen, the swelling starting on the inner side. On examination there was a tense warm effusion, with tenderness all over the knee but maximal over the inner side of the anterior part of the joint line. The range of movement was 175 degrees extension to 110 degrees flexion. Radiographs showed well-marked retropatellar arthritic change. On the history and examination findings a diagnosis of haemarthrosis was made, and this was confirmed by aspiration of 55 ml. of unclotted blood. The right leg was immobilized for a few days in a back splint and then the patient was allowed to carry out active exercises. She regained a full range of movement within five weeks.

Case 3.—This patient, a married woman aged 63, had been under hospital care for arthritis of the knees, hands, and spine since 1947. In February, 1953, she was sent up by her own doctor with a history of having collapsed in the street

Case 4.—Radiograph of the right knee showing minor arthritic lipping behind the lower pole of the patella.

the day before. It was noted that she had a very painful and thickened left knee, and that the joint felt warm. The clinical picture was clouded by a neurotic overlay, so that aspiration was not performed for two weeks. 30 ml. of markedly blood-stained fluid was removed. Two further incidents of bleeding occurred in 1956. Both times aspiration was carried out with rapid improvement in the condition of the knee.

Case 4.—A man aged 50 was seen in June, 1957, with a history of sudden swelling of the right knee occurring when he was standing beside his work bench. There was no causative injury, and the knee seemed to swell in a matter of minutes. An hour before he had been squatting on his heels, but he had felt no pain in the knees. For some years he had experienced "rheumatic pains" in the right knee and hip, and radiographs showed minimal arthritic lipping behind the patella (see Fig.). Aspiration revealed a haemarthrosis. When the case was reviewed some months later the knee was normal apart from the occasional discomfort which the patient had experienced before.

Case 5.—A married woman aged 83 was seen by her doctor on March 2, 1956, with a history of sudden swelling of the right knee without injury. Examination showed the joint to be tensely swollen and warm. At aspiration 65 ml. of unclotted blood was removed. Within a week the knee had returned to its former state. Another incident two weeks later was successfully treated in the same way. *X*-ray films taken about this time showed well-established arthritic changes behind the patella and to the outer side of the joint.

Discussion

The diagnosis of this condition has been made largely upon the history. The story of a rapid onset, tense effusion, without any initiating injury, in a case of osteoarthritis, should make the examiner suspect a spontaneous haemarthrosis. In four of the cases described the radiograph showed fairly marked changes; in all the cases there was *x*-ray evidence of retropatellar arthritis. It has been suggested that the haemarthrosis in arthritis is due to nipping of synovial tags. It is thought that in the present cases the vascular fringe of synovial membrane around the deformed patella may have been involved in this type of injury.

There seems to be little doubt that the best treatment is to aspirate the knee as soon as possible. Smillie (1951) has observed that in massive haemarthrosis the blood in the joint will clot, whereas in the smaller variety the anticoagulant action of the synovial fluid will prevent clotting. Large swellings should therefore be aspirated without delay. It is significant that one patient was thought to be exaggerating her symptoms and valuable time was lost. It is possible that a number of these cases are overlooked and that this condition may be very much more common than was previously thought. Early diagnosis and adequate treatment could reduce its morbidity.

Summary

Five cases of spontaneous haemarthrosis in osteoarthritis have been described.

Points in the diagnosis are discussed.

Early aspiration of the knee is advised.

I am indebted to Dr. A. P. H. Randle, of Garston Manor Rehabilitation Centre, for permission to publish Case 3; to Mr. R. F. O'Driscoll, of Waterford, for Case 4; and to Dr. Peter Guley, of Bushey, for Case 5. I am grateful to Mr. Whitely, of the Photographic Department of the Institute of Orthopaedics, for the reproduction of the *x*-ray film.

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A Guide to Orthopaedics, by T. T. Stamm, is a short, well-illustrated account of the specialty written for the non-specialist. As the author points out, orthopaedics requires team-work from others besides the specialist — medical practitioners, school and public health doctors, physiotherapists, chiropodists, almoners, health visitors, and many others. To all these, and to nurses and senior students, this book provides a useful introduction to the subject. It is published by Blackwell Scientific Publications, Oxford (Pp. 115; illustrated. 12s. 6d.).

IMMUNIZATION DURING PREGNANCY TO THE KIDD (Jk^a) RED-CELL ANTIGEN

BY

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The production of anti-Jk^a as a result of pregnancy is rare. Simmons, Graydon, Jakobowicz, Santamaria, and Garson (1957) have reviewed the literature and described a case of their own. This note reports the finding of a further example of the antibody produced in this way, and demonstrates the importance of using suitable antiglobulin sera in compatibility tests.

Case Report

During her first pregnancy, Mrs. H. was found to be group O, rhesus negative, and her serum was free from immune antibodies; none were detected 10 days after delivery. The techniques used would have detected anti-Jk^a if this had been present. During her second pregnancy the only investigations of her blood were carried out 10 days before delivery. The sample submitted was too small for a full investigation, and on the limited amount of serum available we detected anti-D and anti-C active in saline and albumin. The serum was not tested by the indirect antiglobulin test against known rhesus-negative cells. As Mrs. H. had never been transfused the possibility of yet a third antibody was not considered.

She was delivered of a group O rhesus-positive child. The direct antiglobulin test was positive, and the haematological and clinical findings indicated that transfusion was necessary. Group O, rhesus-negative donor blood was matched against the mother's serum by saline, albumin, and antiglobulin techniques, and the cells of one donor were found incompatible by the antiglobulin technique. Other donors were compatible, and the baby was treated and progressed well. The blood samples of the parents and their baby were submitted for further investigation.

Further Serological Investigations

Red cells.—Mrs. H.: O, MNS, P_1−ve, cde/cde, kk, Le(a+b−), Lu(a−), Fy(a+), Jk(a−), Wr(a−). Mr. H.: A_1, MsNs, P_1−ve, CDe/cde, kk, Le(a−b+), Lu(a+), Fy(a−), Jk(a+), Wr(a−). Baby H.: O, CDe/cde, direct antiglobulin test positive. (Examined at a later date and found to be Jk(a+) when the antiglobulin test was negative.)

Serum.—The presence of anti-D and anti-C active in saline and albumin was confirmed, and examination against a panel of cde/cde cells suggested that the serum contained the immune antibody anti-Jk^a active by the antiglobulin technique, but completely inactive in saline and albumin media (see Table).

		Rhesus-negative Cells		
		Jk(a+)	Jk(a−)	
Mrs. H.'s serum	Positive ..	13	0	$p=\frac{1}{8568}$
	Negative ..	0	5	

Further examination of the anti-Jk^a showed it active with ficinized cells, weakly active with trypsinized cells, but completely inactive with papainized cells. Where enzyme-treated cells did react the degree of reaction was not as great as in the antiglobulin test.

As anti-Jk^a has been reported (Stratton, 1956) as occurring in the non-gamma-globulin fraction, Mrs. H.'s serum was further examined. To anti-human-globulin serum was added a solution of gamma-globulin (1 in 50) so that the serum would no longer agglutinate rhesus-positive cells coated with incomplete anti-D. With this prepared anti-human-globulin serum it was possible to demonstrate that this anti-Jk^a was not a gamma-globulin. Prepared anti-human-gamma-globulin showed Mrs. H.'s anti-D and anti-C to be a gamma-globulin. Tests with a series of commercially available anti-human-globulin sera used at the dilutions recommended by the manufacturers were most unreliable for detecting the anti-Jk^a. Some of these reagents were reliable only for detecting gamma-globulin-type antibodies.

In all the tests the serum had complement present, or this was added to it as fresh human serum, as it was found that the reactions were stronger with complement than without.

Summary and Conclusions

A case is reported in which anti-Jk^a was present as well as the rhesus antibodies anti-C and anti-D. The only stimulus was pregnancy.

The anti-Jk^a was in the non-gamma fraction, and, unless the anti-globulin serum used had antibodies against globulins other than gamma-globulins, the anti-Jk^a could not be detected.

The presence of complement enhanced the reactions of the antibody. Similar experiences have been found with anti-K, anti-Le^a, and anti-Fy^a, and demonstrate the importance of using fresh serum for compatibility tests and of using antiglobulin serum capable of detecting the non-gamma-globulin-type antibodies.

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EIGHT FURTHER CASES OF RADIATION-INDUCED CANCER

BY

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In 1902, six years after the discovery of *x* rays, the first report of a radiation-induced cancer appeared in the literature (Frieben, 1902). It concerned an *x*-ray technician who developed a squamous-celled carcinoma on the dorsum of the hand.

At first, radiation-induced carcinoma was seen only in *x*-ray or radium workers, but in recent years most cases have occurred in patients who have had radiotherapy for malignant or benign conditions, and especially the latter. This is so because these patients live long enough to allow malignant change to take place; young developing tissue seems more susceptible to the carcinogenic effect of ionizing radiation (Clark, 1955), and the method often used in treating those conditions, by protracted multiple exposures, is accepted as the most potent method of inducing radiation carcinoma. Thyrotoxicosis was one of the conditions treated in this fashion (Barclay and Fellows, 1927).

Other benign conditions commonly treated by radiotherapy were haemangiomata, psoriasis, prurigo, pruritus, and lupus vulgaris.

Skin is the commonest site for radiation-induced carcinoma. Other sites reported include bone (Jones, 1953), mediastinum (Pettit *et al.*, 1954), thyroid (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955), stomach (Olson *et al.*, 1956), pharynx and larynx (Goolden, 1951, 1957), and tongue (Deller, 1951). The induction of leukaemia following *x*-ray therapy for ankylosing spondylitis is a special problem and has been fully reviewed by several authors, including Court Brown and Doll (1956).

Most radiation-induced growths are squamous-celled carcinoma, but osteogenic sarcoma, fibrosarcoma, and basal-celled carcinoma have all been reported.

The latent interval for radiation-induced carcinoma varies enormously; two years (Dunlap, 1957) is the shortest, and 49 years (Mitchell and Haybittle, 1955) the longest interval on record.

A description of eight further cases of radiation-induced carcinoma is given.

Case Reports

Case 1.—The patient was a married woman aged 66. From 1924 to 1926 *x*-ray therapy was given for thyrotoxicosis. The treatments were multiple and were given at frequent intervals. In 1948 a warty growth was removed from the neck. Histological examination showed it to be a squamous carcinoma. In 1957 she complained of a lump in the throat—this was more noticeable during swallowing, but there was no real obstruction. She was referred to hospital on May 8, 1958. Examination revealed atrophy of the skin on the anterior aspect of the neck (see Fig.). The mucous membranes of mouth and tongue were normal. There was no koilonychia. The blood count was normal. A direct laryngoscopy revealed a haemorrhagic fleshy mass in the post-cricoid region 15–18 cm. from the incisor teeth. Biopsy showed squamous carcinoma. A soft-tissue *x*-ray film showed a mass in the post-cricoid region consistent with carcinoma. The patient was treated on the linear accelerator. The treatment was well tolerated and the reaction was not unduly severe. Five months after completion of treatment she was symptom-free. Indirect laryngoscopy showed oedema of cords.

Case 1. Showing degree of post-radiation atrophy of the skin.

Case 2.—A married woman aged 54 had *x*-ray therapy to the neck in 1930 for over-active thyroid. She attended for treatment three times weekly for 18 months. She was referred to hospital on June 10, 1958, with a five-months history of pain in the left side of the throat made worse by swallowing, and of dysphagia for solids. Examination showed bilateral exophthalmos. The skin on the anterior neck was grossly atrophic. There was no evidence of anaemia or other suggestion of Plummer–Vinson syndrome. Direct laryngoscopy disclosed a fungating ulcerating growth in the post-cricoid region extending round the right lateral wall. Biopsy showed an epidermoid carcinoma, grade II. A soft-tissue *x*-ray film demonstrated the lesion. The blood count was normal. The growth was treated by megavoltage therapy. At the end of treatment a brisk erythema of the skin was present. The patient was able to swallow solids. An *x*-ray film showed marked regression of the growth. Four months later she was symptom-free and could swallow ordinary food.

Case 3.—The patient was a married woman aged 59. In 1913 and again in 1924 *x* rays had been applied to the neck for thyrotoxicosis. In 1928 a further course of radiation was applied over 10 months. The final course consisted of two exposures a week for two months, once weekly for two months, and then once monthly for six months. In 1950 she complained of a feeling of irritation on the right side of the neck. Later the skin of the neck broke down and subsequently developed into a squamous-celled carcinoma. The lesion was excised and grafted. Histological examination verified the diagnosis. At that time direct laryngoscopy did not show any growth in the pharynx or larynx. She was referred to hospital in March, 1957, complaining of huskiness of voice for two years; over the previous three months her voice had become definitely hoarse. There was a marked telangiectasia of the skin of the neck. A carcinoma was present on the right vocal cord. Biopsy of the cord showed a non-keratinizing well-differentiated squamous-celled carcinoma. On March 14, 1957, a right hemilaryngectomy was performed. The patient's progress continued to be favourable. At the time of writing she was alive and well, apart from huskiness of voice.

Case 4.—A married woman aged 50 had *x*-ray treatment for thyrotoxicosis when aged 25—at first weekly for three months, the course then being repeated. In April, 1949, she complained of pain on swallowing; the pain was referred to the right ear and up the right side of the head. By May difficulty on swallowing was present, and by August she could swallow only fluids. Pain was then constant. On examination her general condition was quite good. Marked telangiectasia and atrophy were present on anterior neck. A mobile gland was found in the right upper cervical group. Direct laryngoscopy showed extensive carcinoma in the post-cricoid region involving the entire right side of the oesophageal inlet and right arytenoid. Biopsy showed carcinoma. On September 14, 1949, an adenoma of the thyroid gland was removed and the tumour in the post-cricoid region was treated by implanting radon seeds. A secondary gland of the neck was excised. Histological report on the gland stated that it was a keratinizing squamous-celled carcinoma. Thyroid tissue showed hyperplasia only. The response to therapy was poor and there was a downhill course—swallowing became impossible and a gastrostomy was performed. The patient died in February, 1950.

Case 5.—A married woman aged 87 had *x*-ray treatment for Graves's disease in 1920; the treatment continued until there was no further evidence of toxicity. She was referred to hospital in July, 1958, with a three-years history of dysphagia. On examination her general condition was bad. A hard fixed gland was present in the right upper deep

cervical region. The skin of the anterior neck showed radiation stigmata. On indirect laryngoscopy there was swelling of the left side of the larynx and pharynx. A soft-tissue radiograph showed in the post-cricoid space a swelling almost certainly a neoplasm. No treatment was given.

Case 6.—A married woman aged 77 had a long course of *x*-ray treatment to the neck for thyrotoxicosis in 1930; she could not recall details. On February 13, 1958, she was referred to hospital. There was a history of six weeks' hoarseness—nothing else. Examination under anaesthesia showed a growth in the right pyriform fossa encroaching on the arytenoid cartilage and right false cord. Vocal cords were normal. The skin of the neck showed minimal changes. A palliative dose of *x* rays was given. In September, 1958, six months after therapy, she was symptom-free.

Case 7.—A married woman aged 69 had *x* rays to the neck for thyrotoxicosis in 1921; the course lasted 18 months—at first twice weekly and then once weekly. In April, 1956, she was referred to a general hospital because of recent loss of weight. Investigations revealed nothing to account for her symptoms. In August she complained of blood-streaked sputum, difficulty on swallowing solids, and cough after food. She was referred to hospital again in November, 1956, when her general condition was found to be bad. An indirect laryngoscopy did not show any growth, but pooling of mucus was present in the interarytenoid space. Both vocal cords were oedematous but mobile. A soft-tissue *x*-ray film of the neck showed what was almost certainly a carcinoma in the post-cricoid region.

Case 8.—When a young girl this patient, a married woman aged 57, was treated for overactive thyroid by *x*-ray therapy. She was referred to hospital in March, 1951, with a seven-months history of increasing difficulty on swallowing solids. The skin of the neck over the thyroid gland showed telangiectasia and atrophy. Oesophagoscopy revealed an infiltrating growth in the post-cricoid region. A radiograph showed a post-cricoid swelling in keeping with the diagnosis of neoplasm.

Discussion

Petersen (1954) reviewed the literature and found references to 200 cases of radiation-induced carcinoma, and he himself added another 21 cases of skin carcinoma to the list. This probably bears no relation to the true incidence of this type of malignancy.

Up to 1956 23 cases of cancer of the larynx and pharynx had been reported as being due to irradiation—five of these had occurred in the larynx and 18 in the pharynx. In 1957 Goolden reported another 18 cases, all in the pharynx, and Cade (1957) reported another four previously unpublished cases—all in the pharynx. The patients were previously treated by *x* rays for thyrotoxicosis, tuberculous adenitis, or syringomyelia. The vast majority were treated for thyrotoxicosis. Only four of the published cases occurred in males—an expected finding, since thyrotoxicosis is mainly a disease of women (8 females to 1 male).

In the present series the longest latent interval was 44 years, the shortest 20: the interval of 44 years is probably the longest on record for a radiation-induced carcinoma of the larynx (Case 3). Previous reports suggested that the latent interval for carcinoma of the larynx was shorter than for pharyngeal growths. For the five cases previously published the mean interval was 13 years.

The number of radiation-induced carcinomata is increasing, mainly owing to the fact that the latent interval has passed and the neoplasms are becoming manifest. Carcinoma of the larynx and pharynx is not a common disease in women, and when a female patient presents with the lesion it is perhaps wise to inquire regarding the application of *x* rays many years before. This is especially to be recommended when a patient presents with a post-cricoid carcinoma without accompanying koilonychia, glossitis, or anaemia.

Not all patients with post-radiation carcinomata show skin stigmata, and seldom does the patient volunteer the information, as she does not connect her symptoms with the previous irradiation.

It will be noted that some of the patients have been treated by radiation—two on the 4 MeV linear accelerator. Perhaps at first sight it would seem hard to reconcile the fact that ionizing radiation is used to treat a radiation-induced growth, but radiosensitivity is not dependent on the causative agent. It is something inherent in the growth itself. Whether or not treatment by irradiation is possible depends on the degree of damage present in the surrounding tissue. Usually it is the skin that has suffered greatest damage, but, even when it is grossly altered, radiation in the 4 MeV range can still be applied, as the physical properties of this energy of radiation cause the maximum dose to be delivered below the skin with little energy absorption at the surface.

Summary

Another eight cases of radiation-induced laryngeal and pharyngeal carcinomata are reported.

All the patients were previously treated for thyrotoxicosis.

Among the eight cases is a carcinoma of the vocal cord, bringing to six the number of true laryngeal carcinomata assumed to be radiation-induced and reported in the literature.

I thank Dr. J. S. Fulton, medical director, for permission to publish the case reports.

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Commonwealth Perspectives (publication No. 8 of the Duke University Commonwealth - Studies Center) is a collection of essays on various aspects of the British Commonwealth. It includes an account of the development of health and welfare programmes in Australia, contributed by Professor B. U. Ratchford of Duke University, Durham, N. Carolina. *Commonwealth Perspectives* (214 pp., 1958) is obtainable in Great Britain from the Cambridge University Press, London, price 34s.

FIVE DUODENAL ULCERS IN A SIBSHIP

BY

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A family tendency to peptic ulceration is not uncommon and much work has been carried out by investigators into the incidence of peptic ulceration occurring in first-degree relationships (Wright *et al.*, 1955). In one survey in North London, the incidence of peptic ulcer occurring in first-degree family relationships was found to be notably raised. The tendency, too, for the same type of ulcer—that is, gastric or duodenal—to occur in these relationships was also increased (Doll and Buch, 1950).

Recent studies have also been made of the incidence of peptic ulceration occurring in twins, although as yet the investigations have not been extensive enough to be of statistical significance (Harvald and Hauge, 1956). In the case of normal brother-and-sister relationship two aetiological factors will obviously be common—that is, genetical and environmental. The former factor will in many cases include an identical blood group, a factor which has already been shown to have some significance in the aetiology of peptic ulceration (Aird *et al.*, 1954). Similarly, the psychosomatic types are likely to be similar in the same family, and this also may be of considerable significance (Hurst, 1924). Such factors as diet, living conditions, smoking and drinking habits, etc., can be regarded as environmental.

An instance of a large family in which four brothers and one sister have all had duodenal ulcers occurred in this area. The mother has a history of many years' indigestion, but has not been in hospital. It is understood that the father is well. There is no blood relationship between father and mother.

History of the Cases

The mother, aged 68, had 15 children ,whose ages now range from 20 to 50 years. There were six girls and nine boys. One of the sons died soon after birth, another was killed as a child in a road accident, and a third died on active service during the war, from wounds. Of the six remaining sons two, whose ages are 40 and 47, are alive and well, with no suggestion of peptic ulceration.

Apart from the sister who had a duodenal ulcer, all the others are alive and well, although one sister, aged 28, has periodic asthmatical attacks. None has any ulcer symptoms. Apart from the ulcers, the whole family seems to enjoy extremely good health.

The first member of the family to be treated surgically for a duodenal ulcer, Mr. A. Z., aged 38, had a perforated ulcer in 1944. He had at that time a history of only four months' indigestion. After a repair operation he was symptom-free for a further five years until he had a second perforation. A further repair operation was carried out, but he continued to have attacks of pain, and in 1951 a partial gastrectomy of the Polya type was carried out. At operation a large chronic duodenal ulcer was found. His post-operative course was satisfactory and he has remained well since.

The second member of the family to come under our care was the youngest brother, Mr. B. Z., aged 25. He was admitted to hospital in March, 1958, as an emergency case with severe abdominal pain in the left hypochondrium. He gave a history of several attacks of this pain during the previous six months, none of which had been so severe as the attack which brought him into hospital. The symptoms and signs on admission were not suggestive enough to make a specific diagnosis, and they subsided under conservative treatment. Subsequently we carried out a barium-meal *x*-ray examination which showed considerable delay in stomach-emptying and a strong suggestion of a duodenal ulcer. Shortly after the *x*-ray examination the patient had a severe haematemesis which necessitated a blood transfusion. Three days later he had a further haematemesis. A Polya partial gastrectomy was then carried out and a large duodenal ulcer was found. The patient made a full recovery and has remained well.

The third member of the family with an ulcer, Miss C. Z., aged 28, came under our care a month later. She had a history of epigastric pain extending back for the previous six years, and had been treated medically in hospital on two occasions. In 1957 a barium-meal *x*-ray examination had shown the presence of an ulcer crater on the posterior wall of the duodenum and, as her condition had not improved for several months, it was decided that partial gastrectomy would be advisable. At operation—a Roux en Y partial gastrectomy—an ulcer was found on the posterior wall of the duodenum. She has remained well since this operation was carried out.

In June, 1958, the eldest of the brothers, Mr. D. Z., aged 49, who gave a history of five years' indigestion, was operated upon. A barium-meal *x*-ray examination in May had shown some degree of pyloric stenosis and the patient was anxious for surgical treatment. At operation two ulcers were, in fact, found—a large gastric ulcer on the posterior wall of the stomach and a small duodenal ulcer near to the pylorus. A high Polya partial gastrectomy was therefore carried out. His post-operative course was satisfactory and he has remained well.

Yet another brother, Mr. E. Z., aged 33, had been treated medically for indigestion for the previous 10 years. Two years ago his symptoms became more severe and a barium-meal *x*-ray examination showed the presence of a duodenal ulcer. He continued, however, with medical treatment, but a repeat *x*-ray examination in September, 1958, showed no improvement. In January, 1959, he was sent to the surgical out-patient department. He was becoming tired of continuous medical treatment and, as his symptoms appeared to be getting worse, it was felt that he too would benefit from gastrectomy. Accordingly he was operated on early in February and a large chronic duodenal ulcer was found. A partial gastrectomy of the Polya type was carried out. It is too soon to assess the results, but his immediate post-operative condition was very satisfactory.

Comment

Intensive efforts have been made to find common factors amongst the family that might be of significance regarding the aetiology of the ulcers. All the affected members had the same blood group, which was A-positive. At some time or other all have been engaged in driving occupations, with some irregularity in their meal-times. One member, D. Z., said they were brought up as a " frying-pan " family, but this was not confirmed by the others. None were heavy smokers, although all did smoke, and their drinking habits were all moderate. None gave the impression of being the hypersthenic, anxious, emotional type suggested by Hurst as being more ulcer-prone. There was nothing of significance in their previous illnesses.

It is interesting to note that with the exception of Mr. A. Z., all the other siblings had their operations carried out within a period of 12 months. Miss C. Z. and Mr. D. Z. had a similar length of history, but B. Z.'s history dates only a few months. However, he was the first of the family to have partial gastrectomy. One is tempted to conclude that the good results obtained from this operation helped to persuade his brothers and sister to have surgical treatment as well.

Another interesting point is the ratio of four males to one female having a duodenal ulcer. Numerous investigations have shown that the sex incidence shows a far greater percentage of duodenal ulcers occurring in the male than in the female, the average being in the region of 80% male.

Summary

A family is described in which duodenal ulcers occurred in several members. Five of the family—four brothers and one sister—had partial gastrectomies. Apart from a direct family relationship, no other common factor has been found which might be significant in the aetiology.

I thank Mr. J. Ewart Schofield, consultant surgeon, and Dr. P. H. Denton, consultant physician, for their permission to publish this report, and Mr. J. Ewart Schofield for his helpful criticism.

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Medical Memoranda

Carotenaemia Occurring in a Case of Anorexia Nervosa

Carotenaemia occurs when excessive amounts of carotene are ingested, in diabetes mellitus, in hyperlipaemic conditions, and in myxoedema; and Cohen (1958) described a "unique case" which he believed to be due to an inborn error of metabolism. Carotenaemia has not previously been reported to occur in anorexia nervosa, and the following case is described in order to draw attention to the possible association.

CASE HISTORY

An unmarried woman of 28 was seen in March, 1958, complaining of anorexia and amenorrhoea since the age of 16½. She had attended various hospitals in the past, with only temporary increase of weight each time. She weighed 7 stone (44.5 kg.) and was 5 ft. 6½ in. (169 cm.) tall.

On examination there was general emaciation, the breasts were small but developed, and the hair distribution was normal. There was no hypertrichosis. The skin was dry, thin, and inelastic, and acrocyanosis was pronounced. A faint yellow tinge of the skin was noticed, although the cyanosis made this less obvious than it would otherwise have been; it was especially marked over the palms and soles, which were bright orange, and to a less extent around the nose and in the axillary folds. The conjunctivae and mucous membranes were clear; the urine was a pale clear yellow and contained no urobilinogen or bile salts. Direct questioning revealed that she had first noticed the yellowness in February, since when it had fluctuated in intensity but never completely gone. The skin had not itched and she had not bothered about it. For the past 10 years she had eaten large amounts of fruit and cooked green vegetables (but never raw carrots), and there had been no recent change in this habit. She had been mildly constipated all her life, but took no aperients or liquid paraffin. Carotenaemia was diagnosed, and was confirmed by finding a serum carotene level of 240 μg./100 ml. (normal 50–120 μg.). The serum vitamin-A concentration, 182 I.U./100 ml. (normal 80–130), was also higher than normal.

There was no evidence of diabetes, a glucose-tolerance test was normal, and the blood cholesterol was 200 mg./100 ml. Clinically she was euthyroid. The B.M.R. was −1%, and the radioactive iodine uptake and excretion were within normal limits. Liver-function tests, plasma protein values, urine, and blood showed no abnormality. She was treated with strict bed rest, green vegetables were omitted from her high-calorie diet, and fresh fruit was restricted. The yellow pigmentation, although fluctuating, remained; and on discharge, after eight weeks as an in-patient, she weighed 8½ stone (54 kg.), the serum carotene was 180 μg./100 ml., and the vitamin A concentration 140 I.U./100 ml.

COMMENT

Carotene is present in variable amounts in many plant materials and in butter and egg yolk (Harris, 1955). It cannot be synthesized by animals and is utilized by them in the formation of vitamin A. This conversion occurs mainly in the intestinal mucosa and to a less extent in the liver, and in some species there is evidence that the absorption of carotene varies directly with thyroid activity (Wright, 1952). Cohen (1958) states that 4–8 lb. (1.8–3.6 kg.) of raw carrots must be eaten daily for some months before carotenaemia appears clinically and that the pigmentation disappears in two to six weeks when the diet is corrected. It seems unlikely, therefore, that the carotenaemia in this case is due to excessive intake, especially in view of the fact that her dietary habits have not altered recently. Pigmentation, as in other states of cachexia, has been described in anorexia nervosa (Berkman, 1930), but this is a brownish colour and obviously very different from the colour and distribution of carotenaemia. Yellow pigmentation of the nails was described in starving Dutch patients in 1944–5 (*Malnutrition and Starvation in Western Netherlands*, 1948), but the skin was said to be sallow, with dun-brown pigmentation. Metabolism is often depressed in anorexia nervosa, although it was not in this patient, but myxoedema does not occur and the serum cholesterol is usually normal.

Cohen described a case of carotenaemia, for which no cause could be found, in a woman of 38 who had had a yellow tinge to her skin for several years, most pronounced on the palms and soles but also affecting the lips and buccal mucosa. In this case the serum carotene was raised and there was vitamin-A deficiency. In addition the patient had lost weight. The case reported here differs in that the serum vitamin-A concentration is high. But large amounts of vitamin A, sufficient for at least six months' deprivation, are normally stored in the liver, and since the carotenaemia in this case is of only three months' duration, while Cohen's patient had had carotenaemia for several years, this may explain the difference. Alternatively, the abnormality may involve a different process. In any case, the possibility that this abnormality is associated with weight loss is interesting, and seems worthy of further investigation.

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Reviews

TUBERCULOSIS IN FIVE VOLUMES

Handbuch der Tuberkulose. Edited by J. Hein, H. Kleinschmidt, and E. Uehlinger. Volume 1: Allgemeine Grundlagen. (Pp. 832+xvi; illustrated. DM. 178.) Stuttgart: Georg Thieme Verlag. 1958.

The target of this comprehensive textbook, the harbinger of five volumes, is to establish itself as an international reference work on tuberculosis. With this object in view the collaboration of many well-known workers outside Germany has been enlisted, among them Löffler of Zurich, Suter of Gainsville, U.S.A., Bloch of Pittsburgh, U.S.A., and Hedvall of Sweden. The German contributions are likewise of the first water, but nevertheless one regrets the absence of any British authority.

Tuberculosis is a widespread disease of universal social and economic significance. The last decade has witnessed stupendous changes in the control, management, and mortality rate of the disease in Western Europe; in fact, in many parts of the world. The incidence of the disease is closely related to social and economic conditions, but the decline in mortality rate is a deceptive index, less accurate than the morbidity rate, which still remains high.

Certain basic principles, for the most part universally accepted, are enunciated and discussed, and the persistent need for radical preventive measures, in spite of all modern advances, is not diminished. The organism, the *Mycobacterium tuberculosis*, in its human and bovine types, is pathogenic to man, who possesses an inherent resistance to the infection with a tissue sensitivity to tuberculo-protein measured by the skin reaction to tuberculin. Recovery from a primary infection is known to produce a degree of acquired resistance to subsequent infections. The dramatic results of combined and prolonged chemotherapy have undoubtedly removed its dread stigma, and the tuberculous subject now has a greater expectation of life than ever before.

There is a fascinating and comprehensive chapter on the history of tuberculosis by Professor Löffler, who traces its existence to prehistoric times, finds it described by ancient civilizations, and pursues our growing knowledge of it to the present antibiotic era. The biology of the tubercle bacillus, tuberculosis and allergy, infection and immunity, sources and modes of spread of infection, primary tuberculosis, hypersensitivity, epidemiology and statistics, tuberculosis and environment in its widest sense, tuberculosis in relation to age and race, the comparative pathology in animals, are among other subjects surveyed and considered.

The production of the book and its many illustrations is unimpeachable. Some of the opinions expressed may be unacceptable in Great Britain, but they are sufficiently authoritative to be worthy of consideration. The extensive bibliography exemplifies the remarkable industry and thoroughness that have gone into the preparation of this book. It is perhaps permissible to wonder whether such a work can profitably be extended to five volumes, but this first tome will indeed preclude any potential complacency in relation to tuberculosis.

PHILIP ELLMAN.

MALIGNANT NEOPLASMS

Cancer. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Volume 4. (Pp. 532+23+ix; illustrated. 85s.) London: Butterworth and Co. (Publishers), Ltd. 1958.

This volume dealing with the clinical aspects of cancer will be valuable to everyone in practice, whether specialist or general practitioner. In 34 chapters and 532 pages the signs, symptoms, diagnosis, operability, general lines of treatment, and the prognosis of malignant growths occurring in every part of the body are adequately described by surgeons who in every instance are authorities on the type of disease they describe. Details of technique are not given, but there are excellent discussions as to the best treatment to be adopted in any particular case. In the account of that curious condition argentaffinoma there is a description of the serious effects of the hormone serotonin, but the remarkable cardiac effects which sometimes occur are not described.

There is a preliminary chapter on the grading or staging of cancer. This has sometimes been based upon microscopical evidence and at other times upon clinical manifestations, and there has been no generally accepted system. Mr. Harmer makes a strong plea for the adoption of the T.N.M. system, which is based on the clinical characteristics of the Tumour, the condition of the lymph Nodes, and the presence or absence of Metastases. This system has the merit of being an accurate clinical appraisement, and many will agree with the conclusion that "the T.N.M. system will serve a useful purpose when it has become generally adopted."

ZACHARY COPE.

METABOLIC DISEASES

Metabolic Disturbances in Clinical Medicine. Edited by G. A. Smart, B.Sc., M.D., F.R.C.P. (Pp. 358+vii; illustrated. 45s.) London: J. and A. Churchill, Ltd. 1958.

This is an interesting book of rather unusual pattern. No attempt has been made to be comprehensive. The editor has chosen only a few subjects for discussion in monograph style. Each article is written by a different expert according to his own ideas on the subject, most being, however, on the clinical level of description. Most of endocrinology has been deliberately omitted on the grounds that it is adequately dealt with elsewhere. The reassortment of medical facts following such a metabolic classification is stimulating. For instance, the chapter on "Disturbances of Metabolism affecting the Central Nervous System" is refreshingly different from the more usual and inevitably rather dry article on diseases of the central nervous system, and gives one the impression of looking at a rapidly expanding subject. Thank goodness! A rather briefer article gives an account of various cardiac diseases of metabolic origin, and other articles deal, among other things, with the haemopoietic system, electrolytes, bone diseases, and kidney and liver disease. The book is a useful addition to the literature of the less exotic metabolic disorders.

C. E. DENT.

ALLERGY IN THE U.S.A.

Practical Allergy. By M. Coleman Harris, M.D., F.A.C.P., and Norman Shure, M.D., M.S., F.A.C.P. (Pp. 471+xiii; illustrated. 52s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1957.

The authors set out to present a comparatively simple textbook on the practical management of allergic problems for doctors who are not experts in this field and for senior medical students. Their text is based

on experiences in teaching senior medical students at the College of Medical Evangelists, Los Angeles.

The details of the different techniques of skin testing are well and fully presented, as is the advice on when and how to carry out desensitization. The detection and management of food allergens follow conventional and accepted lines, and the authors quite properly point out the marked divergence of opinion among different workers in the United States on the frequency of food allergies.

The chapters on history-taking and on the emotional factors in allergic diseases are pleasant reading in which there is much sound advice. Naso-respiratory allergy, insect allergy, physical allergy, various miscellaneous manifestations of allergy, the collagen diseases, and specific and non-specific treatments are all briefly described and discussed.

A very small, but to English readers a not unimportant, part of the book is a table of "Important Allergenic Plants of the British Isles." Apart from the grasses, a formidable list of 65 species or genera is published. It is lists such as these which have confronted and confused beginners in allergy for the last 15 to 20 years. It is unfortunate that the authors are not apparently aware of the atmospheric pollen studies conducted in Britain, for the list could, with benefit, be considerably reduced. In general, however, the book succeeds in giving a very fair and reasonable account of the United States viewpoint on allergic problems, and as such can be recommended to those for whom it is written.

D. A. WILLIAMS.

CLINICAL PATHOLOGY OF THE BLOOD

Laboratory Medicine—Hematology. By John B. Miale, M.D. (Pp. 735; illustrated. £5 2s. 6d.) London: Henry Kimpton. 1958.

This book is intended to be one of a series on laboratory medicine and to be followed by others on chemical pathology and microbiology. The first 360 pages deal with the normal and pathological anatomy and physiology of the blood-forming tissues. In the middle of this section, rather like the jam in a sandwich, is a series of 36 case histories which are shown with the details of the case on one side of the page and pictures of the blood and marrow smears, sections from biopsies, etc., on the opposite page. The next 130 pages deal with disorders of the red cells, and they are followed by sections of about half this length on the white cells and on haemostasis and blood coagulation. There is an appendix of nearly 100 pages on methods. The book is well illustrated with good diagrams and black-and-white photographs and there is plenty of tabulated material. There are five colour plates each containing 24 pictures about 30 mm. square, but the quality of these pictures is poor. Clinical aspects of haematology are cut to a minimum, and there is practically nothing about treatment. The book contains much accurate and well-documented information about the blood-forming organs, with emphasis on the dynamic aspects of erythropoiesis. Of the four audiences to whom the author addresses himself—medical student, clinician, pathologist, and medical technologist—it will be most useful to the two last, for it is essentially a book on the clinical pathology of the blood. The writing is agreeably simple and clear, and each chapter is headed by a quotation, of which that on haemolytic anaemias is one of the most apt: "Some men give their blood to their country; others their spleen."

L. J. WITTS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Chemistry of Industrial Toxicology. By Hervey B. Elkins. 2nd edition. (Pp. 452+xi; illustrated. 92s.) New York: John Wiley and Sons Inc. London: Chapman and Hall, Ltd. 1959.

Klinische Psychopathologie. By Kurt Schneider. 5th edition. (Pp. 166+viii. MD. 12.80.) Stuttgart: Georg Thieme Verlag. 1959.

Le Cœur. Volume II. ***Les Maladies Organiques du Cœur. Le Cœur dans les Maladies.*** By Professor Camille Lian and his pupils. (Pp. 278; illustrated. 2,000 Fr.) Paris: L'Expansion Scientifique Française. 1959.

Chest and Heart Disease in the Commonwealth, 1958. Transactions of the NAPT Commonwealth Chest Conference, incorporating the Annual Conference of the British Tuberculosis Association. London, 1st-14th July, 1958. (Pp. 443; illustrated. 35s.) London: Chest and Heart Association. 1959.

Geographic Ophthalmology. Asia, Australia, and Africa. Edited by William John Holmes, M.D. (Pp. 293+xv; illustrated. 63s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Bronchography. By C. Dijkstra, M.D. (Pp. 157+ix; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1959.

Experimentation in Man. By Henry K. Beecher, M.D. (Pp. 80. 25s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The Management of Emergencies in Thoracic Surgery. By John Borrie, M.B.E., Ch.M., F.R.C.S.(Eng.), F.R.A.C.S. Foreword by Sir Russell Brock. (Pp. 340+xi; illustrated 84s.) London: Staples Press. 1959.

Crime Doctor. The Memoirs of a Police Surgeon. By A. David Matthews. (Pp. 228; illustrated. 18s.) London: John Long. 1959.

Early Diagnosis. By various authors. Edited by Henry Miller, M.D., F.R.C.P. (Pp. 400+viii. 25s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

Abnormal Haemoglobins. A Symposium Organized by the Council for International Organizations of Medical Sciences. Edited by J. H. P. Jonxis, and J. F. Delafresnaye. (Pp. 427+ix; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1959.

Total Surgical Management. By James D. Hardy, M.S., M.D., F.A.C.S. (Pp. 292+x; illustrated. $9.50.) New York and London: Grune and Stratton. 1959.

Medical Museum Technology. By J. J. Edwards and M. J. Edwards. (Pp. 172+ix; illustrated. 21s.) London: Oxford University Press. 1959.

Textbook of Surgery. Edited by H. Fred Moseley, M.A., D.M., M.Ch.(Oxon.), F.A.C.S., F.R.C.S.(Eng.), F.R.C.S.(C.). 3rd edition. (Pp. 1,336+xxi; illustrated. £6 7s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Surgical Pathology. By Lauren V. Ackerman, M.D., in collaboration with Harvey R. Butcher, jun., M.D. (Pp. 1,096; illustrated. £5 12s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Coma Diabeticum. Seine Pathophysiologie, Pathogenese, Symptomatik und Therapie. By Professor Rudolf Baumann, M.D. (Pp 210; illustrated. DM. 25.70.) Berlin: VEB Verlag Volk und Gesundheit. 1959.

Science, Medicine and Morals. A Survey and a Suggestion. By Charles E. Raven, D.D., D.Sc., F.B.A. (Pp. 189. 15s.) London: Hodder and Stoughton. 1959.

Beiträge zur Modernen Therapie. Vorträge und Diskussionsbemerkungen der ersten drei Weimarer Therapietagungen, 1955, 1956, 1957. Edited by Peter G. Hesse, M.D. (Pp. 498+xii; illustrated. DM. 38.25.) Jena: VEB Gustav Fischer Verlag. 1959.

The Kansas Doctor. A Century of Pioneering. By Thomas Neville Bonner. (Pp 334; illustrated. $5.) Lawrence: University of Kansas Press. 1959.

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NEW ATTACK ON BREAST CANCER

The surgical ablation of certain endocrine glands can induce regression of growth in approximately 50% of cases of metastatic breast cancer, but not more than 25% remain in regression for longer than a year. Similar results can be obtained in some cases by treatment with an androgen. It is becoming fashionable to think of the cells which compose the primary, secondary, or metastatic foci of growth in breast cancer as being of two kinds. When tumours respond promptly to endocrine ablation and remain in regression for a relatively long time, the large majority of their cells are believed to be hormone-sensitive, and a small minority of the cells hormone-insensitive and independent. Proliferation of cells in this insensitive minority eventually produces a clinically recognizable recurrence. Breast cancers which completely fail to respond to endocrine ablation presumably consist almost entirely of hormone-insensitive cells. The length of time for which regression can be induced by endocrine ablation or by hormone therapy is therefore determined by the ratio of hormone-sensitive to hormone-insensitive cells, and there is no obvious reason for supposing that hormone-sensitive cells are transformed into insensitive cells, though the tumour as a whole may pass from the dependent to the independent state. This may be an unjustifiable simplification, but it disposes of another purely hypothetical and remarkably pessimistic argument—that hormone-sensitive cancer cells strongly tend to become hormone-insensitive as the disease progresses, thus becoming increasingly invulnerable.

Our only weapon against hormone-insensitive cells that cannot be excised or destroyed by surgery or radiotherapy is chemotherapy. Published results suggest that the most effective compounds are the alkylating antimitotic agents derived from nitrogen mustard. The rates of regression of growth in metastatic breast cancer induced by these compounds are disappointingly low and appreciably smaller than those induced by the administration of testosterone. Drugs of the nitrogen mustard group are, without exception, exceedingly lethal to the haemopoietic marrow, and it is probable that their effective dose is proportional to the number of surgically inaccessible cancer cells they are expected to kill. This number will be minimal if, during the administration of the drug, the proliferation of hormone-sensitive cells is held in check by the administration of an appropriate hormone. Furthermore, the menace of marrow aplasia will be lessened if the disease is attacked in its early or middle stages before the total weight of the metastases is unmanageably large.

These general considerations have led Mr. G. Whyte Watson and Dr. Robert L. Turner, of the Royal Infirmary, Bradford, to treat a series of 34 patients suffering from breast cancer by the simultaneous administration of testosterone and "thiotepa," an alkylating antimitotic drug which, when given alone, is known to kill the cells of breast cancer. Oophorectomy was carried out before treatment in pre-menopausal patients. Their preliminary report appears at p. 1315 of the *Journal* this week. It suggests that combined therapy by male hormone and antimitotic drug may eventually increase the percentage of artificially induced remissions in cases of breast cancer and, it is to be hoped, increase their duration also.

This careful clinical trial, which has clearly entailed much labour, reveals that testosterone administered simultaneously with thiotepa defends the bone marrow to some extent against the lethal effects of the alkylating agent, thus permitting the administration of larger doses and increasing its oncolytic action. Watson and Turner make the interesting suggestion that it may be possible to synthesize a compound in which testosterone is linked with the cytocidal ethyleneimonium grouping of thiotepa.

IMMUNIZATION SCHEDULES

Recent letters in this *Journal* have shown the existence of widespread uncertainty on the most suitable methods of immunization in childhood. This has been particularly bewildering to general practitioners at a time when they are taking an increasing part in the poliomyelitis vaccination scheme. The findings of the Wellcome symposium on immunization appearing elsewhere in this issue (p. 1342) are therefore timely, and the recommendations should go a long way towards removing existing confusion. All interests concerned with the subject were strongly represented in the symposium, and the findings must carry great weight.

[1] Parish, H. J., *Brit. med. J.*, 1959, **1**, 640.

The part of the report that will be of most general interest is that giving complete programmes of immunization during childhood years. A choice of two schedules is offered, and the advantages and disadvantages of each are discussed. It is left to the doctor to decide whether to take advantage of the shorter course of the triple vaccine with the slightly greater risk of post-inoculation poliomyelitis or to use the longer course with single prophylactics. Both schedules accept the importance of giving whooping-cough vaccine early in life in order to provide the maximum protection to very young babies. When whooping-cough vaccine is given early in the form of the triple prophylactic some interference with the response to diphtheria toxoid may occur in some babies, but this deficiency will be remedied by the reinforcing dose at the age of 15 to 18 months.

With the increase in the number of diseases to be prevented there is growing complaint about the number of injections that a child has to receive. An attempt has been made to reduce the number of visits the doctor has to pay by recommending that two procedures be carried out at the same visit whenever immunological considerations allow.

Hitherto it has been customary to encourage smallpox vaccination in the first year of life in the belief that post-vaccinal encephalitis and other complications were less common at that time than at later ages. One of the papers given at the symposium showed by an analysis of official data that complications are less common between 1 and 5 years of age than in infancy. The recommendation is that smallpox vaccination may be given at any suitable time before the age of 5 years. Each doctor will place vaccination at the point in his schedule which he thinks most appropriate.

Tetanus prophylaxis is provided in both schemes, and this underlines the urgent necessity of providing for each child a personal record of immunization which will be readily available if the child suffers an injury. This question has been widely discussed,[1] but the possibility of a large increase in the number of children immunized against tetanus makes action a matter of urgency, and there will be no quarrel with the recommendation in the report that personal record cards should be issued. It is a mistake to think that tetanus prophylaxis is the only justification for personal records. When families move their home, and often on other occasions, there is much delay in obtaining immunization records. Personal records can be invaluable in such circumstances.

There was a discussion on the method of sterilizing syringes and needles, and it is recommended that a sterile syringe and needle must be used for each injection. The general acceptance of this will necessitate changes in existing routine in many places. Though these may take some time to bring about, there can be no doubt of the wisdom of this advice.

It is to be hoped that notice will be taken of the recommendation to set up a representative body to keep problems of immunization under review. Many aspects of the subject require further study, and in this there must be close co-operation between clinicians and laboratory workers. The symposium undoubtedly succeeded in its main purpose, which was to give authoritative guidance that would be generally acceptable and result in uniformity in practice.

CONJOINED TWINS

Both the public and the profession have heard much in recent months about Siamese or conjoined twins. Naturally questions have been asked about the causes of this dramatic phenomenon and whether there has been an increase in its occurrence. In the opening pages of this issue Professor Ian Aird gives an account of several pairs of living and stillborn conjoined twins and discusses theories of their origin.

Biologists have generally accepted that conjoined twins are the result of incomplete separation of the organizing centres in a single cleaving egg or blastoderm. Had complete separation occurred then monozygotic twins would have resulted. G. W. Corner[1] has described the three phases in early human development when monozygotic twinning could occur. The first phase is when the blastomeres (daughter cells) of a two-cell ovum might separate to form two embryos each with its own chorion. Corner states that genetico-anatomical analyses "agree in pointing to blastomere separation as the method of embryonic duplication in about one-third of all cases of single-ovum twinning." The second phase is reached when duplication of the inner cell mass of the blastocyst gives rise to twin embryos enclosed within a single chorion but each possessing its own amnion and, usually, its own yolk sac. Early embryonic stages showing such duplication have been described in a sheep blastocyst[2] (the earliest known mammalian single-ovum twin, reported by R. Assheton in 1898), in that of a pig,[3] and in human material.[1 4–6] The third phase is entered when the embryonic rudiment of the germinal disk becomes duplicated or, technically, when double gastrulation occurs. Two embryos will develop in one amniotic cavity and will have a common yolk sac. This condition is well known in embryos of lower

[1] Corner, G. W., *Amer. J. Obstet. Gynec.*, 1955, **70**, 933.
[2] Assheton, R., *J. Anat. (Lond.)*, 1898, **32**, 362.
[3] Streeter, G. L., *Amer. J. Anat.*, 1924, **34**, 183.
[4] Heuser, C. H., *Anat. Rec.*, 1954, **118**, 310.
[5] Morton, W. R. M., *J. Anat. (Lond.)*, 1954, **88**, 572.
[6] Potter, J. C., *Anat. Rec.*, 1927, **34**, 253.
[7] Willis, R. A., *The Borderland of Embryology and Pathology*, 1958, London.
[8] Needham, J., *Biochemistry and Morphogenesis*, 1942, London.

vertebrates, but has been seen only rarely in human embryos. Corner[1] includes in his article an illustration of an embryonic double monster 28–30 days old and describes others in which the arrangement of amnion and yolk sac strongly suggests that conjoined twins are formed late in the period covered by the three phases (about 15 days). It is, however, inevitably difficult for obstetricians to be sure of the early arrangement and fate of the foetal membranes by examination of specimens at term.

Professor Aird provides other evidence suggesting that most conjoined twins are uniovular, but he also postulates that they may result from union of separate blastomeres, a speculation advanced by others. Corner has investigated claims for fusion and disappearance of apposed layers of either chorion or amnion and considers it doubtful if such ever occur. "If any significant number . . . had been dichorionic, then some of the twin pairs would have been bisexual"; and none has yet been recorded. Professor Aird gives an example of Chinese conjoined twins who, he suggests, may have been of different sex, though the evidence is not convincing. Conjoined twins are usually slightly different, even to the extent of one having a cleft palate or other abnormality. An explanation for this dissimilarity is that the lateness of development of embryonic duplication in the three phases outlined above allows asymmetrical cellular differentiation to occur before twinning, and thus perhaps unequal sharing of material and potential at twinning.

The literature concerned with experimental production of twinning in lower vertebrates is now considerable.[7 8] Over-ripeness or staleness of the ovum, arrest of development through cooling or oxygen lack, and action of other external factors have been cited as potential causes of double monsters. Yet knowledge is still lacking about the causes of conjoined twinning in mammals. The advances of surgery in separating human conjoined twins underline the need for further investigations, not only by embryological observation and experiment, but also by more careful study of living survivors. There is yet no conclusive evidence that the incidence of conjoined twinning is increasing, but the suggestion that it occurs more frequently in one country—Nigeria—is worthy of further inquiry.

REFLEX MUSCULAR SPASM

The misfortunes of war provided the opportunity for Henry Head and G. Riddoch to study the effects of injury to the spinal cord.[1 2] This resulted in their well-known description of reflex activity in such patients. Another war provided further opportunities for study, and some of the earlier ideas were developed or modified.[3–5]

The following sequence of events takes place after physiological or anatomical transection of the spinal cord in man.[2] Immediately after injury there is total muscular flaccidity below the lesion. This is the period of spinal shock. This state of flaccidity may be prolonged by sepsis or by further trauma, such as surgical operations, and any state of debility. The patient then passes through a period of minimal reflex activity into one characterized by flexor spasms of the limbs and tonic contraction of other muscles (bladder, bowel, abdomen). This state may be seen after about six weeks, and was named the "mass reflex" by Head and Riddoch. The most evocative area is the sole of the foot, stimulation of which often causes violent flexion of the limb, followed at once by flexion of the opposite leg; there is evacuation of the bladder and bowel, and an accompanying outburst of sweating. The response is diffuse and massive. The stimulus is non-specific, for the reaction can be evoked by stimuli elsewhere below the segmental level of the injury. The reflex is self-propagating, and if preventive measures are not taken[6] the limbs and body develop inflexible contractions. Pressure sores appear, not only where the body is supported, but where the limbs are in contact, and even between the knees and chest.

At this stage there may be other self-propagating reflexes, some causing spasm of the bladder wall and external urethral sphincter, giving rise to back pressure in the ureters and kidneys, and others affecting the bowel and anal sphincter, leading to faecal impaction. If damage to these structures can be avoided,[6 7] an automatic bladder may be established.[1] The bladder empties reflexly when 100–600 ml. of urine has collected; instead of contracting with the bladder wall, the external urethral sphincter relaxes and efficient evacuation is achieved. It is now known[4] that the flexor state is not final, but is followed by one in which mixed flexor and extensor spasms occur, and later by one in which the spasms are predominantly extensor. In contrast to these, 12% of cases of transection of the spinal cord remain in a state of flaccid paraplegia. The reason for this is not clear, but may be associated with damage to peripheral nerves or the conus medullaris.

When the cord lesion is incomplete the picture may be less clear-cut. Voluntary activity may be retained to some degree, though it is often of little use because of the violent spasms it evokes. Some sensory fibres may remain intact, with the result that the spasms may not only be violent enough to fling the patient from a chair, but are also extremely painful. Such a patient fears any stimulus which may elicit the reflex, even though it may be as slight as the touch of a sheet or a vibration of the room.

Attempts have been made to reduce the motor response by various means, including anterior rhizotomy. D. Munro and other workers have carried out this operation,[8 9] though Sir Geoffrey Jefferson was

[1] Head, H., and Riddoch, G., *Brain*, 1917, **40**, 188.
[2] Riddoch, G., ibid., 1917, **40**, 264.
[3] Scarff, J. E., and Pool, J. L., *J. Neurosurg.*, 1946, **3**, 285.
[4] Kuhn, R. A., and Macht, M. B., *Bull. Johns Hopk. Hosp.*, 1949, **84**, 43.
[5] —— *J. nerv. ment. Dis.*, 1951, **113**, 301.
[6] Guttman, L., *Brit. J. phys. Med.*, 1946, **9**, 130.
[7] Munro, D., *The Treatment of Injuries to the Nervous System*, p. 284. Philadelphia. 1952.
[8] —— *New Engl. J. Med.*, 1945, **233**, 453.
[9] Freeman, L. W., and Heimburger, R. F., *J. Neurosurg.*, 1947, **4**, 435.
[10] Munro, D., and Spatz, E. L., *New Engl. J. Med.*, 1959, **260**, 1.

actually the first to perform it. If the eleventh thoracic to first sacral anterior roots (inclusive) are divided, bladder and bowel action is not further impaired, but there is no possibility of any future function in the lower limbs. Nevertheless such patients may manage to walk with the aid of callipers and crutches. Other operations have been devised,[8] such as resection of the stump of the spinal cord and posterior chordotomy, but none have provided a final solution to the problem. It is heartening, therefore, to read a preliminary report of a less drastic measure which has proved successful in three cases.

Munro[7] suggested that if the vicious circle between stimulus and muscular response could be broken, even temporarily, the massive reflex might not occur. This idea was successfully applied to the treatment of spasm of the detrusor muscle and external urethral sphincter by injecting the second to fourth sacral roots and the internal pudendal nerves with 2% procaine. This has given permanent relief of spasm in 50 cases, though 15–20 injections were sometimes necessary. The method has now been applied by Munro and E. L. Spatz[10] to the treatment of patients with severe reflex spasm who retain some voluntary power. Anterior rhizotomy was not possible because of the loss of function which would have ensued. These workers found that when one sciatic nerve was injected there was immediate relief of spasm in both legs. In the first case—one of partial lesion of the cord at D 9–10—it was necessary to repeat the injection on the original side, and to inject the opposite nerve four times. Pudendal and sacral blocks were performed to control micturition. The patient has now been free of spasm for a year, and has normal function of bladder and bowel. Intractable spasms have been similarly treated in two patients whose arms were affected. Munro and Spatz recommended that the first injection should be performed under direct vision, the target being marked with a silver clip to allow subsequent injections to be made percutaneously with radiological control.

INTRA-ARTICULAR STEROID THERAPY

The local use of steroids to suppress some of the effects of inflammation is now well established in dermatology, in asthma, ulcerative colitis, and in rheumatology. The great advantage of local as against systemic application is the very much higher concentration that can be reached—concentrations, in fact, that would be impossible to maintain by systemic administration without disaster. The main disadvantage of intra-articular steroid therapy is the necessity of entering the joint with a needle. While in life-endangering diseases like diabetes and pernicious anaemia the prospect of continued regular injections is borne with fortitude, the fortnightly needling of rheumatoid joints which is usually necessary with hydrocortisone is both daunting to the patient and irksome to the physician. Nor is it without risk. Joints affected by rheumatoid arthritis are prone to infection, and steroids seem to decrease resistance thereto. It is, in fact, surprising that infection is so seldom seen. G. N. Chandler and his associates[1] have recently drawn attention to another danger, that of accelerated bone destruction. It might perhaps be expected that the greater use of the joint allowed by the abolition of pain would lead to the development of a Charcot-like state.

Some of the disadvantages of this form of treatment would undoubtedly disappear if a steroid preparation could be found which needed only relatively infrequent injections—that is, one with a prolonged effect due to slow release within the joint cavity. In last week's issue of the *Journal* Drs. W. R. Murdoch and G. Will[2] described their experience with prednisolone trimethylacetate, a potent compound of comparatively low solubility. They gave 20 mg. in a microcrystalline suspension (2 ml.) at weekly intervals to 27 patients with rheumatoid arthritis and to a few patients with other disorders, and found a rapid effect on pain and swelling and great functional benefit in the majority of cases. They also found that prednisolone trimethylacetate decreased the white-cell count in the synovial fluid and increased its viscosity—as had been previously reported to occur with hydrocortisone, but to a less extent—and, in addition, brought about a fall in protein concentration towards normality. No direct comparison was made with the effects of hydrocortisone. M. Thompson[3] and J. H. Glyn and D. R. L. Newton[4] on less extensive experience felt that there was little difference between the two substances given by intra-articular injection. However, if Murdoch and Will's results, clinical and biochemical, are contrasted with those previously reported for hydrocortisone, prednisolone trimethylacetate would appear to compare favourably with the earlier steroid.

[1] Chandler, G. N., Jones, D. T., Wright, V., and Hartfall, S. J., *Brit. med. J.* 1959, **1**, 952.
[2] Murdoch, W. R., and Will, G., ibid., 1959, **1**, 1267 and 1271.
[3] Thompson, M., ibid., 1957, **2**, 294.
[4] Glyn, J. H., and Newton, D. R. L., *Ann. phys. Med.*, 1958, **4**, 176.

TELLING THE PARENTS

The realization that their child is mentally backward is likely to be a shock to the parents. They will probably be emotionally upset and feel the need to adjust themselves to the facts. The doctor's task in such cases is not easy. The diagnosis may not at first be clear, and observation over a period of time is perhaps necessary. The parents may not yet be ready to face the situation and may, for instance, try to seek other more reassuring opinions; they can, when realization comes, tend to feel that they have not been handled with sufficient tact.

Dr. C. H. Waskowitz, of the Johns Hopkins Hospital, Baltimore,[5] interviewed 40 parents of retarded children to try to establish retrospectively how the parents first suspected backwardness, whom they consulted about it,

[5] *J. Pediat.*, 1959, **54**, 319.
[6] *Amer. J. ment. Defic.*, 1959, **63**, 696.
[7] *Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency*, 1957, H.M.S.O., London.

and who really told them. The information he obtained showed how hurtful the news had often been and how the parents had varied in their reactions, including the speed at which they were ready to accept it. The need for a skilful appreciation of their feelings by their doctor was emphasized, both by those parents who were grateful for the way in which they were told and by parents who were not. Time was necessary to take in the extent of their problems, to overcome the anxieties that arose, and to find answers to the many questions on care and management. Thus more than one consultation was usually required.

J. L. Schulman and S. Stern,[6] also working from the Johns Hopkins Hospital, have pointed out that medical people are often reluctant to inform parents of the child's degree of retardation. These authors consider it may be due partly to lack of confidence in the tests used to ascertain the degree of retardation, but more often to fear of the parents' reaction to such news. They asked the parents of 50 retarded children, aged 3 to 12 years, before diagnostic testing, to estimate the developmental age of their child. They found some correlation between the child's performance of intelligence tests and the parents' estimate, and considered that there was no basis for the belief that parents are often unaware of the retardation before seeking help. However, they considered that the awareness was sensed rather than clearly understood, and the parents' estimate was then a useful springboard for discussion of the whole problem. These children tested by Schulman and Stern were, it seems, old enough for the parents to have had sufficient experience of them to form an opinion; the parents of younger children may not be so accurate in their estimates.

The Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency[7] suggests in paragraph 687 that diagnostic clinics for severely subnormal children should be set up where the staff would give skilled diagnostic help and continue to offer advice to parents over the years. This would meet some of the emotional difficulties that parents of retarded children may now experience. But they would not free doctors referring subnormal children to the clinics for investigation from their prior task of telling the parents why they are doing so.

GLUCOSE-TOLERANCE TESTS

The finding of glycosuria in the absence of symptoms of diabetes necessitates further investigation in the form of a glucose-tolerance test. For most purposes the oral test, in which 50–100 g. glucose is given and blood-sugar estimations made during the next two hours, is adequate.[1] If the fasting, peak, and two-hour values for blood sugar are raised, then there is no difficulty in making a diagnosis of diabetes. Similarly if the curve is normal in spite of the presence of glycosuria the condition can be confidently labelled as renal glycosuria. A certain proportion of patients, however, will be found to have glucose-tolerance tests which lie between these two extremes and it is by no means clear how they are to be interpreted. In Britain[2] particular attention is paid to the two-hour value, figures in excess of 100 mg. "true" glucose per 100 ml. being regarded with suspicion: such a view has been strengthened by W. P. U. Jackson's studies of prediabetes.[3] Peak values above 180 mg. per 100 ml. are attributed to rapid intestinal absorption if the two-hour figure is near normal, but E. P. Joslin[4] does not recognize this "lag" type of curve as a separate entity, and regards the height of the peak rather than the two-hour value as evidence of potential abnormality.

Various attempts have been made to devise a more satisfactory test for unmasking the potential diabetic. The intravenous glucose-tolerance test overcomes the factor of intestinal absorption, but there is evidence that it is not very sensitive.[1] The diabetogenic action of steroids has been used with some success, a large dose of cortisone being given prior to the test.[5,6] Recently the whole problem of tolerance has been re-examined, with particular reference to the significance of the "lag" curve, in Royal Air Force personnel sent for investigation of glycosuria.[7,8] Tests were done with galactose (to determine the effect of intestinal absorption), glucose, and cortisone plus glucose. The authors found that there was normally an inverse relationship between the peak and two-hour values for blood sugar. On the basis of galactose-tolerance tests subjects with "lag" curves could be divided into two groups. The first had a high galactose peak, similar to that found in patients after partial gastrectomy, but a normal inverse relationship for glucose. In the second group the galactose curve was flat in spite of a high glucose peak, and the two-hour value for glucose was high normal (80–105 mg. per 100 ml.). The latter type of response was believed to indicate impaired tolerance, and this view was supported by the finding of frankly diabetic curves in a small proportion of subjects with "lag" curves who were retested after an interval of several years. The cortisone-modified glucose tolerance test was disappointing in that only one among the subjects classified as potential diabetics gave a positive response.

The conclusion that may be drawn from these various studies is that minor abnormalities in the two-hour glucose value should be viewed with suspicion, even in the presence of a "lag" curve. The problem of detecting early impairment of carbohydrate tolerance is not merely an academic one, since dietary adjustment and weight reduction may prevent a permanent breakdown. Unfortunately the lack of agreement on what constitutes abnormal tolerance is reflected in the variety of methods that have been used for its detection, and there is a need for a simple standardized technique which would be acceptable to all workers in the field.

[1] Moyer, J. H., and Womack, C. R., *Amer. J. med. Sci.*, 1950, **219**, 161.
[2] Lawrence, R. D., *Med. Clin. N. Amer.*, 1947, **31**, 289.
[3] Jackson, W. P. U., and Woolf, N., *Lancet*, 1957, **1**, 614.
[4] Joslin, E. P., Root, H. F., White, P., and Marble, A., *Treatment of Diabetes Mellitus*, 1952, 9th ed., Philadelphia.
[5] Fajans, S. S., and Conn, J. W., *Diabetes*, 1954, **3**, 296.
[6] Duncan, L. J. P., *Quart. J. exp. Physiol.*, 1956, **41**, 453.
[7] Dische, S., Stamm, W. P., and Goudie, R. B., *J. clin. Path.*, 1958, **11**, 350.
[8] Goudie, R. B., Stamm, W. P., and Dische, S., ibid., 1958, **11**, 428.

SIR ARTHUR CONAN DOYLE, LL.D., M.D.

BORN MAY 22, 1859

A Biographical Note by

MAURICE CAMPBELL, O.B.E., M.D., F.R.C.P.

Arthur Conan Doyle was born at Edinburgh on May 22, 1859. His grandfather moved from Dublin to London and became a well-known caricaturist: his three elder sons all became equally well known in literary and artistic circles, Richard illustrating *The Newcomes* and designing the cover of *Punch*. The fourth, Charles, Arthur's father, became a civil servant, though he spent his spare time painting. He married Mary Foley, also of Irish parentage: she traced her descent from the Plantagenets and instilled Arthur with a love of chivalry and of history. She must have been a capable woman, for Charles's salary was £240 a year, and on this she managed to bring up a large family.

Arthur was sent to school to Stonyhurst, but was not happy or successful. His strict upbringing was perhaps one reason why he lost his Roman Catholic faith. In October, 1876, he started as a medical student at Edinburgh University. He still spent much of his time reading his favourite authors—at first tales of adventure and later the romances of Scott and the historical essays of Macaulay. He was good at most games and was always ready for a fight. He had little money and was keen to help his mother, as his sisters were already doing. During some long vacations he worked as an unqualified assistant, which took him to Birmingham and to London, and in 1880 as "surgeon" to a whaling expedition, for which he earned £50 and the lasting respect of the mate for his prowess as a boxer. More important for his future, he had already earned three guineas for a story in *Chambers's Journal*.

At Edinburgh

One of his teachers at Edinburgh was Dr. Joseph Bell, whose powers of observation and deduction—so essential in all medical diagnosis—made a great impression and gave him some ideas for Sherlock Holmes. In spite of all his interests he must have worked hard, for he graduated M.B., with credit if not with distinction, in August, 1881. For the next six months he was on the west coast of Africa as a ship surgeon.

On his return he was invited to join Dr. Budd, who had been a fellow-student and was now in practice at Plymouth. Budd appears to have been a maniacal enthusiast, full of energy and wild ideas, and the practice must have been one of the most curious and unethical that has been known. Conan Doyle always had the highest moral standards in his medical and in his private life and found it impossible to work with his friend, so that there were many rows, and once at least a fight, and he left after six months. Some of Budd's qualities were reproduced in different characters in his tales.

In Practice on His Own

He decided to start practice on his own at Southsea, and chose an area where he thought there might be a shortage of doctors. But patients were a long time coming, and during the eight years he was there (July, 1882, to December, 1890) he earned no more than £300 a year from the practice. In 1885 he married Louise Hawkins, whose brother had been one of his patients. He had many friends and activities and was captain of the cricket club and secretary of the literary and scientific society, to which he read several papers.

I find it hard to understand why Doyle was not a great success in practice. He was fond of his fellow men and understood them, though perhaps he idealized women and understood them less; and he had a good knowledge of medicine, as I have tried to show in my "Sherlock Holmes and Dr. Watson: A Medical Digression," published in the *Guy's Hospital Gazette* in 1934. It is doubtful if the works of any other novelist describe extrasystoles, oedema due to fibrillation, angina pectoris, aneurysm, rheumatic valve disease, and left ventricular failure with orthopnoea with such careful adherence to medical probabilities. I can only think that in a town such as Southsea, and perhaps elsewhere, it was impossible to build up a good practice without purchasing one.

Early Writings

During these eight years he was writing hard, though too frequently his stories were returned to him. *The Study in Scarlet* appeared in *Beeton's Xmas Annual* in 1887 and the *Sign of Four* soon after. *The Firm of Girdlestone* and *Micah Clark* and many other tales were finally published during this time: in spite of their popularity later they did not lead to immediate success or fame, and during the period he never earned more than about £50 a year from his writings. For those who feel that he wrote the Sherlock Holmes adventures in close collaboration with Dr. Watson, it is interesting to speculate how they met. While he was at Southsea Dr. James Watson, M.D.Edin., was secretary of the local medical society; there are indications that he may have been an elder brother of Dr. John Watson and may have invited him down to one of the society's medical dinners.

Setting up as an Eye Specialist

Conan Doyle decided to leave Southsea to set up as an eye specialist, and was given a farewell dinner on December 12, 1890. By January 5 of the next year he was at Vienna to study ophthalmology. By March 24 he was back in London, and two weeks later settled at 2, Devonshire Place, where, as he said, "he waited in the consulting room and no one waited in the waiting room"; and within two months he had decided to give up the practice of medicine and devote himself to writing.

Literary Success

I cannot think that a man of such great common sense as Doyle really took this incursion into ophthalmology very seriously. I think he must have almost decided earlier, and the literary success that came to him during these months enabled him to put his dearest wish into action. *The White Company* was appearing in *Cornhill* and most of *The Adventures of Sherlock Holmes* were written at Devonshire Place and soon appeared in the *Strand Magazine*. These led to wide recognition of Conan Doyle and of Sherlock Holmes, and Doyle got to know many more writers and henceforth moved in literary rather than in medical circles.

In June, 1891, the family moved to South Norwood, where they lived till 1897, when they built a house at Hindhead. But in 1893 Mrs. Doyle developed tuberculosis of the lungs and they moved to Switzerland for the winter, where in 1895 Doyle introduced skiing. He had carried out his first lecture tour in America the previous year. He was writing all the time, and the *Memoirs of Sherlock Holmes* (1892–93), *Stark Munro Letters*, *Exploits of Brigadier Gerard* (1895), and *Rodney Stone* (1896) belong to this period.

South African War

In 1899 Doyle went to the South African war in charge of a hospital unit. He wrote what was probably the best and fairest history of the South African war and a shorter

pamphlet that was translated into many languages, and did much to counteract the anti-British feeling that was widely spread over the continent at that time. Partly for this, perhaps, in 1902 he was knighted and appointed Deputy Lieutenant for the County of Surrey. He was still writing exciting and popular stories, and *The Hound of the Baskervilles* (1901–2), *The Adventures of Gerard* (1902–3), *The Return of Sherlock Holmes* (1903–4), and *Sir Nigel* belong to this period.

His wife lived till 1906, though at first she had been given a very bad prognosis. In the same year he read the statement of Edalji, the Parsee solicitor who had been condemned to penal servitude for horse-maiming three years before. He was at once convinced of his innocence and studied the evidence until he was able to force the appointment of a committee of inquiry that set Edalji free. His other well-known case that led to the relief of Slater after 18 years in prison was an example of his sympathy for those who had suffered injustice rather than of his powers of observation and deduction that had been shown in the Edalji case. He was always anxious to fight for the weak, and his attacks on the injustices in the Belgian Congo were not without effect.

Second Marriage

He was married again in 1907, to Miss Jean Leckie, whose family he had known for several years, and they went to live at Crowborough in Sussex. The marriage was exceptionally happy, and two sons and a daughter were added to the son and daughter of his previous marriage: Conan Doyle had reached a position where he was more able to relax with his children. He became interested in the theatre and lost much money in staging a version of *Rodney Stone*, but recovered it with a dramatization of *The Speckled Band*.

During the 1914–18 war he wrote *The British Campaign in France and Flanders* (6 vols.) and was disappointed that it was not more popular. He could still write enthralling stories, as shown by *His Last Bow* and *The Valley of Fear*, which appeared in the *Strand Magazine* between 1911 and 1915. The last of the Sherlock Holmes stories did not appear till 1926, but in general opinion these are not as good.

Last Years

After the war, when he was nearly 60, spiritualism, which had attracted him for many years, became his main interest and occupation. He gave up nearly everything for it and lectured in America and many other countries. Even after he had suffered from a cardiac infarct he would not let this interfere with his work. I admire above all the courageous patient, and I like the story of his reply to the consultant who said he could not carry out his lecture tour: "I did not come here to ask you to arrange my life for me but to tell me how I can avoid another attack during my tour."

He died in July, 1930, aged 71, a simple friendly man who admired courage and honour and integrity, and exemplified these virtues in his life. There are enthusiasts for his tales of boxing, like *Rodney Stone*, for his historical novels, and for the tales of Brigadier Gerard, but not so many as there are for the tales of Sherlock Holmes and Dr. Watson. He will, I think, live as one of the great story-tellers, and I like to think that his medical experiences were some help to him in this.

[I should like to acknowledge my debt in writing this article to Hesketh Pearson's *Conan Doyle: His Life and Art*.]

Mr. Kenneth Walker's *The Story of Medicine*, first published by Hutchinson Ltd. in 1954, is now available in a cheap edition (Arrow Books Ltd., 178, Great Portland Street, London, W.1. Pp. 326; illustrated. 5s.). The book provides a short history of medicine written in a style suitable for the layman, and covering the period from prehistoric and Greek times to the present.

IMMUNIZATION IN CHILDHOOD

A symposium on "Immunization in Childhood" was held in the Wellcome Building, London, from May 4 to 6. Sponsored by the Wellcome Foundation, the symposium was organized by an independent steering committee,* under the chairmanship of Brigadier Sir JOHN BOYD, F.R.S., which assembled about 70 participants representative of the many branches of medicine interested in the practical aspects of immunization. It was a declared object of the conference to try to resolve conflicting viewpoints and to recommend acceptable immunization schedules for general use in Britain. While most of the members were British, a few experts from W.H.O., Commonwealth countries, the U.S.A., and France also took part.

The full proceedings of the symposium will be published later in the year by Messrs. E. and S. Livingstone Ltd. Here we report the first two sessions—on "The Risks of Immunization" and "Poliomyelitis and Pertussis"; and, with the approval of the steering committee, the full and authorized text of the "Recommendations" agreed upon by the conference. The "Recommendations" include two alternative practical immunization schedules. For reasons of space we are unable to include an account of the third and fourth sessions—on diphtheria and tetanus immunization, combined prophylactics, "personal records," and the pros and cons of immunization schedules—but these topics are dealt with in the conference's final "Recommendations."

Sir John Boyd's Address

The symposium was opened by Sir JOHN BOYD. A number of diseases resulting from bacterial or viral infection could now be prevented by means of vaccines or toxoids, and the problem of administering these to the best advantage, and with the least inconvenience to the recipients, had become complex and difficult, he said. The time had come to assess all the evidence and work out a scheme—or schemes—which would serve as a guide, or perhaps even a model, for those who had to administer these immunizing agents. The symposium had been organized for that purpose.

They had at the symposium representatives of all sections of the profession interested in the subject—medical officers of health, school medical officers, general practitioners, paediatricians, epidemiologists, statisticians, representatives from infectious diseases hospitals, from the Services, from the laboratories, from interested departments overseas, and, casting a paternal eye on the proceedings, from the Ministry of Health. He welcomed them all. Among the many distinguished visitors he would like especially to mention Dr. Salk, whose name was now a household word.

HAZARDS OF IMMUNIZATION

"Provocation Poliomyelitis"

Dr. JOHN KNOWELDEN (Department of Epidemiology and Medical Statistics, London School of Hygiene) gave a paper on "Provocation Poliomyelitis," which he said was first recognized in 1949. A Medical Research Council committee had sponsored a large investigation of the problem in Britain, and on the basis of information collected in the years 1951–4 had confirmed the observations of earlier workers that there was sometimes an association between the site of injection and the limb paralysed in children who developed poliomyelitis within 4 weeks of inoculation with diphtheria prophylactics or pertussis

*The Steering Committee was as follows: Sir John Boyd, F.R.S. (chairman), Dr. W. C. Cockburn, Dr. D. G. Evans, Dr. B. E. Schlesinger, Dr. I. Taylor, and Dr. H. J. Parish (secretary).

vaccine alone or in combination. The committee had in addition been able to make an estimate of the size of the risk, which they found was at its maximum in the second and third quarters of the year. Taking all prophylactics together, one associated case of poliomyelitis developed for every 37,000 inoculations given.

The risk was not the same with each antigen. It was greatest with mixed diphtheria-pertussis vaccine containing alum, where it was estimated that one case of paralysis occurred with every 15,000 injections. Significant but smaller risks were observed with A.P.T., P.T.A.P., and mixed diphtheria-pertussis vaccine without alum. No significant risk was found after plain pertussis vaccine, T.A.F. or formol diphtheria toxoid, or smallpox vaccine. The most disturbing observation was that there was a significant risk with alum-free diphtheria-pertussis vaccine. Studies in Canada, where alum-free diphtheria-pertussis vaccine and alum-free diphtheria-pertussis-tetanus vaccine were used, failed to show any association between the site of injection and the limb paralysed. This important difference between the findings in the two countries was difficult to explain.

Dr. W. C. COCKBURN (Central Public Health Laboratory) said that in 1958 a further study of the problem had been begun by the Epidemiological Research Laboratory at the Central Public Health Laboratory, in collaboration with medical officers of health in England and Wales. The number of observations was still small, but the picture emerging was consonant with that given in the Medical Research Council report referred to by Dr. Knowelden, and triple antigen was behaving similarly to alum-free mixed diphtheria-pertussis vaccine. Dr. L. B. HOLT (Wright-Fleming Institute) said that he had used another method of analysis of the Medical Research Council data. On the whole he confirmed the published findings, except that pertussis vaccine was not free from risk as had been suggested. On the other hand, he did not find that the addition of formol diphtheria toxoid to pertussis vaccine increased the risk.

Dr. IAN TAYLOR (London County Council) said that the estimates of the dangers of alum-free mixed prophylactics were based on very small numbers. In one Division of the London County Council where special records were kept 70,000 injections of triple antigen had been given without ill-effect. In the London County Council area as a whole between 1956 and 1958 a quarter of a million injections of triple antigen had been given with apparent safety. Dr. A. M.-M. PAYNE (World Health Organization) said the question of provocation poliomyelitis might be of importance if living attenuated poliomyelitis vaccine was taken into general use, as injections of other prophylactics—or of drugs—might precipitate paralysis in the recently vaccinated. He described an outbreak of poliomyelitis in 1956–7 in Samoa, where nearly all the cases were in children injected with a long-acting penicillin preparation a short time before the onset of illness.

Pertussis Vaccine Encephalopathy

In discussing "Other Hazards of Immunization," Dr. W. C. COCKBURN said that, though no injection was free from risks, diphtheria and tetanus toxoids were very safe. His paper was concerned mainly with pertussis vaccine. He said more than 100 cases of pertussis vaccine encephalopathy, which was manifested by convulsions and coma and sometimes hemiplegia and severe mental deterioration or death, had been reported in the last 25 years. The syndrome had been observed after any injection in the course and after most types of pertussis vaccine. The pathogenesis was unknown. Besides this very serious but very rare condition, some children developed uncomplicated febrile convulsions from which recovery was complete.

After contrasting the risks of pertussis vaccination with the risks of the disease itself, he said that so long as the incidence of pertussis remained high the risk of encephalopathy (which could not be measured, but might be less than one in a million or one in 10 million) should not be considered a contraindication to vaccination. When the incidence of pertussis had been reduced to a low level by vaccination the risks of vaccination would assume greater prominence in the minds of parents, and in these conditions the occurrence of a case of encephalopathy with all its tragic consequences might receive great publicity and turn parents against vaccination. As encephalopathy seemed to be due to some peculiar property of the pertussis bacillus or to a predisposition in the child affected, he urged the need for a full study of every case which was reported and of laboratory studies of the bacillus in an effort to obviate the risk as soon as possible. As the aetiology was at present unknown, steps to avoid the occurrence of cases could not be formulated, though it was clear that if one injection of pertussis vaccine caused symptoms in the central nervous system no more injections should be given. In addition, on purely general grounds he thought children with a previous history of repeated convulsions should not be injected, and children suffering from other illnesses should not be injected until they had fully recovered.

Dr. L. J. M. LAURENT (Hither Green Hospital) said he had seen several small children who became pale and almost cyanotic a few hours after vaccination and who developed curious screaming fits. All had so far recovered, but he thought these attacks were a definite effect of the vaccine.

Hazards of Smallpox and Polio Vaccination

In discussing the hazards of smallpox vaccination Dr. G. WYNNE-GRIFFITH (Anglesey) said he had analysed the available information on generalized vaccinia and post-vaccinal encephalitis occurring between 1951 and 1957 in England and Wales, Scotland, and parts of Northern Ireland. After primary vaccination the rate of generalized vaccinia was 51 per million in children below 1 year of age and 23 per million in children 1–4 years of age. For post-vaccinal encephalitis the rate was 15.8 per million in children below one year of age and 2.1 per million for children 1–4 years of age. These figures showed that the recommended age of primary smallpox vaccination should be reconsidered.

Dr. D. H. GEFFEN (St. Pancras) discussed the risks of poliomyelitis vaccination and said that over 200 million injections had been given in the world without reports of serious hazards. The Cutter disaster of 1955, when children developed poliomyelitis from live virus in the vaccine, had not been repeated. Allergic manifestations, so far not serious, had been mentioned recently. Some were due to penicillin in the vaccine and some probably to sensitivity to other components. Other illnesses reported were probable chance associations in time, and poliomyelitis vaccine could continue to be used without anxiety, except perhaps in persons known to be penicillin-sensitive.

Sterilization of Syringes and Needles

Professor J. W. HOWIE (University of Glasgow) discussed sterilization of syringes and needles. He said that boiling at its best was relatively safe, but in practice short cuts were taken which made it dangerously ineffective. Immersion in alcohol had so many limitations that it was unjustified if any alternative was available. Hot oil was also unreliable. Autoclaving was good if done by someone who understood autoclaves, but this was often not the case. Dry heat was the method of choice, since it alone permitted the sterilization of a fully assembled lubricated syringe, which could be stored in a sealed container until required. Conveyer ovens were best for large syringe services.

In his view every inoculation should carry the best possible guarantee of sterility. This would involve radical changes in present practice, but we had sooner or later to face the alternatives of safety or risk. The danger of syringe hepatitis was probably small, but it had not yet been measured. Once it occurred we could do little to control it, nor could we be sure it would always have a

satisfactory outcome. Was sterilization too important to be left in the hands of the inoculator? Should not local health authorities set up a syringe service? Even at fourpence a time, it was not too much to pay for safety. In the future disposable plastic syringes might meet the need, but not yet.

Dr. C. METCALFE BROWN (Manchester) said he had a centralized, dry-sterilized syringe service which, though expensive to set up, worked very satisfactorily. Dr. J. F. WARIN (Oxford) said small authorities could not readily afford such schemes. Professor P. LÉPINE (Paris) said that in Paris a centralized scheme in which syringe and needles were autoclaved worked well. Dr. J. A. SCOTT (London, County Council), said 60 to 100 clinics were held in London daily. Boiling water was available at all clinics, so boiling was the most practical method at present.

Professor T. ANDERSON (University of Glasgow) said he had recently seen three cases of syringe hepatitis from inoculation procedures. This was a more serious disease than some against which immunization was practised. Dr. G. S. WILSON (Public Health Laboratory Service) said that, in contrast to practice in hospitals, where syringes might be grossly contaminated, mass immunization was a relatively clean procedure. So long as syringes and needles were sterilized by autoclaving or dry heat or prolonged boiling before the injection session began, he thought a satisfactory level of freedom from risk could be maintained if they were boiled for 5 or more minutes between injections. Syringes and needles should of course be used once only before being re-sterilized.

POLIOMYELITIS VACCINATION

Type 1 the Problem

Dr. D. G. EVANS (M.R.C., London) introduced the subject and stressed the importance of using adequately potent poliomyelitis vaccine for immunization. Two primary doses of a potent vaccine established a good basal immunity and a third dose 12 months later gave a booster response with persistent antibody levels. Unfortunately, vaccine at present available, although producing a satisfactory response to types 2 and 3, did not always produce an equally satisfactory response to type 1. Consideration should be given to the possibility of overcoming this deficiency by incorporating an adjuvant in the vaccine, and investigations should be made to determine the minimum concentration necessary to produce an enhancing effect.

With potent vaccines, good antibody levels could be obtained in infancy by two primary doses given between 8 and 10 months of age (when there was little or no interference from maternal antibody), followed a year later by a third dose. If it were decided to give the infant triple (diphtheria-tetanus-pertussis) vaccine before vaccination against poliomyelitis, this could be done under the cover of maternal antibody if the pregnant woman had been immunized with poliomyelitis vaccine.

Dr. J. O'H. TOBIN (M.R.C., London) also pointed out, from studies in adolescents, that type 1 was the most unsatisfactory component of the present-day vaccine, and considered that this deficiency could be overcome by a threefold increase of the type 1 component. With such fortified vaccine a good primary response was obtained, antibody was maintained, and the third dose gave a substantial response in a high proportion of subjects.

Age for Primary Immunization

Dr. F. T. PERKINS (M.R.C., London) considered that immunization against poliomyelitis could not be done successfully until 8 to 9 months of age, when there was little or no maternal antibody interference. Even in this age group, the response to the type 1 component of the vaccine was poor after two doses. He found, however, that if three doses were given a more satisfactory response resulted to all three types, and considered that primary immunization of this age group could be successfully carried out using three doses. Dr. J. A. DUDGEON (Glaxo Laboratories) agreed that maternal antibody interfered with the response to poliomyelitis vaccination in early infancy.

Professor G. W. A. DICK (Queen's University, Belfast) briefly referred to immunization with live attenuated poliomyelitis vaccine and said that there was no evidence to suggest that it produced a more durable immunity than inactivated vaccine. He considered that adequate immunization against poliomyelitis could be produced by inactivated vaccines. Dr. ANDRÉ BOUÉ (Paris) presented the results of an investigation with the French poliomyelitis vaccine. He had found that children responded better to the type 1 component than to types 2 and 3.

Dr. J. E. SALK (Pittsburgh) showed that a direct relationship existed between the antibody response to poliomyelitis vaccine and the mass of antigen injected. He had observed antibody levels in children for a number of years after their third booster dose and found that they persisted for at least four years when adequate doses of vaccine had been used initially.

Dr. L. G. GREENBERG (Ottawa), in referring to the possibility of incorporating an adjuvant in poliomyelitis vaccine, pointed out that in Canada only small concentrations of alum were used in toxoids and vaccines. He considered that, in the past, too much alum had been used and that just as good an adjuvant effect could be obtained with smaller quantities. Professor P. LÉPINE agreed with Dr. Boué that the early vaccines prepared in France had been better in the type 1 component than in types 2 and 3. The present vaccines, however, were equally potent in all three types. He added that even with the earlier vaccines children had responded to the booster dose for all three types. He supported Professor Dick's view that the antibody response to live virus vaccine was no better than that obtained with inactivated vaccine.

Mixed Antigens

Professor R. J. WILSON (Toronto) briefly outlined the recommended use of poliomyelitis vaccine in Canada. Two preparations were available—(*a*) diphtheria-tetanus-pertussis-polio vaccine, and (*b*) diphtheria-tetanus-polio vaccine, neither containing adjuvant. The first was given during the first five years of life and the second later. Clinical trials had been made in children of less than 12 months of age; they had received three doses of diphtheria-tetanus-pertussis-polio vaccine, starting at 3 months of age, and one year later a further dose of the same preparation. Good response had been obtained to all three components of the polio vaccine and also to the diphtheria and tetanus toxoids. It was considered that the mixed antigens were stable, and they were at present being widely used in Canada. It was recommended that two reinforcing doses of diphtheria-tetanus-pertussis-polio vaccine should be given at 3 and 5 years, and an additional reinforcing dose of diphtheria-tetanus-polio vaccine during school age.

PERTUSSIS VACCINATION

Dr. W. C. COCKBURN introduced the discussion on pertussis vaccination. He said it was now known to be effective, and a vaccine which had been shown in the laboratory by the intracerebral mouse protection test to be of good potency would reduce the secondary familial attack rate from over 80% to certainly 30%, and probably considerably lower. He recommended that the vaccine used should be a plain suspension of whole pertussis bacilli killed with formalin or "merthiolate" and preserved in merthiolate. Three doses of 1 ml., each containing 20,000 million organisms, should be given. One month at least should elapse between the doses.

Though alum-containing vaccines had been shown to improve agglutinin production in children below 6 months of age, they probably carried a greater risk of provoking poliomyelitis and caused more abscesses than plain pertussis vaccines. Unless they were shown to improve protection

against infection, and not only to improve agglutinin production, they should not be used. As a soluble fraction of the pertussis bacillus, prepared by the late Professor L. Pillemer, had given as good protection as a whole-bacillus vaccine, he recommended more study, both in the field and laboratory, of this and other fractions.

Declining Incidence and Mortality

In a series of tables he showed that both the incidence and deaths from pertussis in England and Wales were falling, and said that in 1958 the number of cases (about 33,000) was less than half that for 1957, and the number of deaths (25) was less than a third of that for 1957. He did not yet know how much of the fall was due to vaccination. Time would show that more clearly. As over one half of the deaths and probably about 5% of cases were in children below 6 months of age, early vaccination was necessary. This was the only common disease preventable by immunization in which administration early in life was necessary. The age of greatest incidence was, however, between 1 and 4 years, and the level of immunity should be high during this period.

Studies had shown that primary vaccination was effective for at least three years. More information was necessary on the need for reinforcing doses at school entry. Even if immunity had begun to wane then, was it better to allow a child about 5 years of age to have a mild attack and develop a strong natural immunity, or to give it another injection and postpone the attack to an even later age? Experience would tell. In the meantime, every effort should be made to vaccinate as many children as possible as early in life as possible.

Professor T. ANDERSON said that deaths from pertussis had been falling since 1940, owing probably to the treatment of respiratory complications with antibiotics. If pertussis vaccine was to be part of a polyvalent vaccine, it should probably not be given until the child was 6 months old. This might not prevent all the deaths but might give better herd immunity. He did not think reinforcing doses necessary. Dr. J. UNGAR (Glaxo Laboratories) said the laboratory testing of fractions of the pertussis bacillus was of great importance. Pertussis vaccine was stable and was unaffected by the addition of other antigens to it. In his studies the level of protection in children was not necessarily parallel with the level of agglutinins in the serum. Alum was unnecessary in whole bacterial vaccines.

Early Vaccination Urged

Dr. L. J. M. LAURENT said that whereas in 1948–52 only 10% of cases admitted to hospital were in children below 6 months of age, in 1953–8 the proportion had risen to 41%. He hoped health authorities would concentrate on vaccinating children below 6 months of age. Dr. R. E. HOPE SIMPSON (Cirencester) said that if pertussis occurred in vaccinated children it was often so mild as to be unsuspected. If unvaccinated babies were exposed to such cases they developed unmodified attacks, which, because they were often very acute, might not be diagnosed in the first instance. This was an added reason for early vaccination. Did mothers transfer passive immunity to babies?

Dr. N. R. BUTLER (University College Hospital, London) said that in a recent study only 20% of cord-blood samples had measurable levels of pertussis agglutinins. There was apparently no interference with the agglutinin response to active immunization in babies with maternal antibodies to pertussis. Professor R. CRUICKSHANK said he thought the notification figures for pertussis were unreliable because only 10% of cases were notified. He thought that the intracerebral mouse test results might not always be wholly reliable, but despite his reservations he strongly urged that children be vaccinated against the disease and that the Ministry of Health be asked to make pertussis vaccine a free issue.

RECOMMENDATIONS*

1. Expectant mothers should be told (*a*) that they should ensure that they themselves have been vaccinated against poliomyelitis; and (*b*) that their children should be vaccinated against whooping-cough, diphtheria, tetanus, smallpox, and poliomyelitis.

Combined Prophylactics

2. The family doctor should ordinarily choose between Schedules "A" and "B" (see Table), and should hand to the mother a printed sheet detailing the chosen schedule, giving the appropriate times for the various immunizations. The doctor should appreciate the advantages and disadvantages of the use of combined prophylactics, which are as follows:

Advantages

(1) Notwithstanding the possibility of immunological interference, many doctors consider that some immunity, obtained when the opportunity is presented, is better than no immunity at all; deficiencies in protective titres are likely to be remedied at the time of the reinforcing dose of triple prophylactic given at some time after the first birthday.

(2) The first six months of life present a good opportunity for commencing immunization procedures against as many important

*These recommendations were agreed to by the symposium.

SCHEDULE A

Age	Visit	Vaccine	Injection	Interval
5 weeks–6 months	1	Pertussis	1	4 weeks or more
	2	"	2	4 weeks or more
	3	"	3	
7–10 months	4	Poliomyelitis	4	4 weeks or more
	5	"	5	
10–12 "	6	Diphtheria and tetanus	6	4 weeks
	7	Diphtheria and tetanus Pertussis	7 8	
15–18 "	8	Diphtheria and tetanus Poliomyelitis*	9 10	
Smallpox some time during the first 5 years				
School entry ..	9	Diphtheria and tetanus	11	
8–9 years	10	Diphtheria and tetanus Smallpox (revaccination)	12	
10–15 " ..	11	B.C.G.	13	

* There is no doubt that a fourth dose of poliomyelitis vaccine will be necessary, but the exact timing of this dose has not yet been decided.

SCHEDULE B

Age	Visit	Vaccine	Injection	Interval
2–6 months	1	Triple (diphtheria, tetanus, and pertussis)	1	4 weeks or more
	2	Triple (diphtheria, tetanus, and pertussis)	2	4 weeks or more
	3	Triple (diphtheria, tetanus, and pertussis)	3	
7–10 "	4	Poliomyelitis	4	4 weeks or more
	5	"	5	
15–18 "	6	Triple (diphtheria, tetanus, and pertussis) Poliomyelitis*	6 7	
Smallpox some time during the first 5 years				
School entry	7	Diphtheria and tetanus	8	
8–9 years	8	Diphtheria and tetanus Smallpox (revaccination)	9	
10–15 ..	9	B.C.G.	10	

* There is no doubt that a fourth dose of poliomyelitis vaccine will be necessary, but the exact timing of this dose has not yet been decided.

diseases as possible. The mother is usually more receptive of advice from her doctor at that time than later. The baby is less upset by inoculations in early life than subsequently: in consequence the mother too is less worried, and, from the psychological standpoint, is more likely to continue with the schedule recommended by her doctor.

(3) There is a reduction in the number of injections.

(4) The reduced number of visits substantially increases the likelihood of the full course being carried out.

Disadvantages

(1) Mixed antigens, even without alum, carry a greater risk of "provocation" poliomyelitis than single antigens.

(2) Some babies may not respond well in the early months of life to active immunization against diphtheria.

Schedules "A" and "B"

3. Schedule "A" is designed to reduce to a minimum such hazards as "provocation" poliomyelitis, which occasionally accompany immunizing procedures. It is as follows†:

(*a*) Three doses of pertussis vaccine should be given between the age of 5 weeks and 6 months—the earlier the better, since whooping cough is most serious during infancy. The minimum intervals between the injections should be four weeks.

(*b*) Two doses of poliomyelitis vaccine between the seventh and tenth months. The minimum interval between these injections should be four weeks.

(*c*) Two doses of diphtheria-tetanus vaccine between the tenth and twelfth months. The interval between these injections should be four weeks.

(*d*) A fourth dose of pertussis vaccine should be given at the same session as the second injection of diphtheria-tetanus vaccine (above), preferably into the opposite arm.

(*e*) A third dose of diphtheria-tetanus vaccine and a third dose of poliomyelitis vaccine‡ should be given between the fifteenth and eighteenth months, preferably at the same session, into opposite arms.

(*f*) Smallpox vaccination should be given some time during the first five years.

(*g*) A fourth dose of diphtheria-tetanus vaccine at school entry.

(*h*) A fifth (small) dose of diphtheria-tetanus vaccine and smallpox revaccination, at 8 to 9 years. Primary vaccination against smallpox is not considered advisable at this time, except in the event of possible exposure to infection.

(*i*) B.C.G. vaccination should be carried out routinely between the ages of 10 and 15 years. (When there has been, or is likely to be, exposure to tuberculous infection, this vaccination is done at any age.)

4. Schedule "B" differs from Schedule "A" in that it includes the use of diphtheria-tetanus-pertussis ("triple") vaccine. It is as follows:

(*a*) Three doses of triple vaccine between the second and sixth months. The minimum intervals between these injections should be four weeks.

(*b*) Two doses of poliomyelitis vaccine between the seventh and tenth months. The minimum interval between these injections should be four weeks.

(*c*) A fourth dose of triple vaccine and a third dose of poliomyelitis vaccine should be given between the fifteenth and eighteenth months, preferably at the same session, into opposite arms.

(*d*) From this stage onwards, this schedule is similar to Schedule "A."

In comparing the above two schemes it should be noted that, from birth to 18 months of age, Schedule "A" comprises 10 injections (made at eight visits), while Schedule "B" comprises seven injections (made at six visits). In return for this effort, useful protection is obtained at an early age against four important diseases of childhood—an important point in discussing immunization with parents.

†None of the antigens mentioned in paragraphs 3 and 4 of the "Recommendations" contains adjuvants.

‡There is no doubt that a fourth dose of poliomyelitis vaccine will be necessary, but the exact timing of this dose has not yet been decided.

(*Continued at foot of next column*)

(*Continued from preceding column*)

Sterilization and Records

5. A sterile syringe and needle must be used for each injection.

6. Personal records of immunization are desirable, and it is essential that they should be readily available in respect of tetanus. Cards, tattooing, and disks all have their merits and disadvantages. Cards should be an official issue, and be standardized. In order to avoid confusion, the abbreviated titles for immunological products, employed in the *British Pharmacopoeia, 1958*, should be widely adopted. Tattooing with a small letter "T" (which is a very simple procedure) on the completion of a course of three injections of tetanus toxoid would be a valuable addition to the system of recording.

7. The general practitioner's National Health Service record card should be modified to allow him to make a separate record of all immunizations. The medical officer of health should be notified of all immunization procedures. There should be a greater exchange of information concerning inoculations performed between parents, general practitioners, and local authorities.

Advisory Body

8. Consideration should be given to the setting up of a body to represent the various interests in immunization. Its function should on the one hand be advisory, with special reference to ensuring reasonable uniformity of immunization schedules, and, on the other hand, it should be able to indicate problems requiring further study.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Diabinese (Pfizer). — This is chlorpropamide, a sulphonamide derivative which has a hypoglycaemic action when given by mouth. It is available in tablets of 100 mg. and 250 mg. The way in which it lowers the blood sugar has not been fully worked out, but it increases production of insulin by the pancreas and may have a more direct action on carbohydrate metabolism in the liver. Its actions and clinical applications are similar to those of tolbutamide, but it is excreted much more slowly. To achieve an adequate blood level, the dose required is smaller and the tablets need only be given daily.

Chlorpropamide may be used for the treatment of middle-aged or elderly diabetics whose disease is mild and who fail to respond to proper dietary treatment. It should not be given to obese patients. It does not control the hyperglycaemia of diabetics who have had significant degrees of ketosis, and is not suitable for the treatment of young diabetics. Some patients of the mild-elderly type may already be on small doses of insulin. Attempts to discontinue insulin and substitute chlorpropamide should be made only under strict supervision and with facilities for urgent blood-sugar estimations if required. The initial dose should be 250 mg. a day, and this should not be exceeded in elderly patients or those of slight build. If necessary the dose may be increased to 500 mg. a day in others. The maximum effect is not seen for five to seven days and full therapeutic response for several weeks. The dose should subsequently be reduced to a minimum maintenance level.

Side-effects so far reported are confusion, giddiness, and headache—usually with doses in excess of those suggested above. True hypoglycaemic attacks may occur. A few cases of jaundice have been reported; clinically and pathologically they resemble chlorpromazine jaundice.

N.H.S. basic price: 100 tabs., 250 mg., 49s. 4½d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical Ethics

SIR,—As a practising physician in psychological medicine I welcome your leading article on medical ethics (*Journal*, May 2, p. 1170). Since most of our patients choose their tea, hair shampoo, and gadgets from T.V., so also do they acquire the facility of relating their illness and my treatment to the authorities featured on television. Not so long ago, when after prolonged consideration and consultation I advised that a patient should undergo an orbital undercutting, I was asked by a deputation of the family if I did not agree that since this was a serious course the opinion of an expert on leucotomy should be sought. I was referred to a certain T.V. programme and I was told the identity of the expert.

I think that T.V. and radio programmes are well done if a highly informed and intelligent *layman* interviews an anonymous specialist who should, in the familiar technique, have only the back of his head—well screened in a winged armchair—shown to the vast audience. If a senior member of the profession, honoured by the Royal Colleges as a Fellow, has become a showman or personality on radio or T.V., surely if the G.M.C. does not act the Royal Colleges should. A pertinent question would be "to what extent have the professional emoluments of the advertising physician been augmented by his T.V. appearances?" In other words to what extent has advertising paid?

That the medium is powerful was brought home to me recently. A practitioner rang me to say he was impressed by my talk on the wireless. I told him I had not broadcast. He said the voice was like mine, but I had also heard the talk on my car wireless (and it was very good), but the speaker was a Scotsman and I am a Welshman. How much more so T.V. appearances! I rely on psychiatric social workers to identify these sepulchral personalities, and, Sir, do they not look sepulchral?

Ethics have got so out of hand that now *patients* are brought into the full glare of publicity with one-sided complaints about their treatments. I was sorry to see a most revered psychiatrist, and lately the most enlightened head of a progressive mental hospital, brought in on the same programme to be given the passing word, "I would like to hear both sides of the story." The terms "the consultant psychiatrist," "physician in psychological medicine," "medical superintendent," indicate to the viewer that in their infinite wisdom the B.B.C. has discovered the rungs of the ladder which lead to the summit. The gullible viewer believes they (or it) must be right. Another fallacy in ethics is that any doctor in full-time State service is not bound to the laws pertaining to doctors in general. Since 1948 medical ethics have deteriorated. But we cannot place the blame squarely on the doctors concerned, the press, or the advertising agencies; it must be shared between the General Medical Council, the Royal Colleges, and of course the doctors concerned. Who would fail to make hay while the sun shines?—I am, etc.,

London, W.1. J. GORDON MATHIAS.

SIR,—During most of two decades of relatively unopposed village practice I have busied myself with the wider aspects of the welfare of my patients through local government, etc. I can speak with experience when I say that the publicity I have received has been more of a handicap to me in my practice than a help. I would have done far better for myself if I had been a Conservative or a Freemason or gone to church regularly, but I have no regrets that I chose the hard way.

It must be remembered that an anonymous doctor cuts no ice and his writing has little authority with a layman. Why are your own book reviews signed? Medical articles in the lay press in any event are more likely to do harm than good, and may be pernicious; whilst letters to attract attention to the medical skill or interests of the writer will surely in a lifetime of practice, general or consultant, defeat their own aim. I am sorry to find you playing the part of *laudator temporis acti*. Each generation of older doctors talks or writes about the deterioration in ethics. When were the golden days? Fifty years ago? Read the *Journal* of the time, when the panel system was being instituted, and see what was written then. Hippocrates certainly had views on the subject, and I expect that so had Celsus and the other worthies. But in general one finds that those who preach the most practise the least, and snarls at another usually arise from jealousy, which was ever the sign of deterioration or inferiority. The average doctor knows how to behave, and does behave: there will always be exceptions.

I think that the General Medical Council is right to adopt a moderate attitude. What matters most is the calibre of the men at the top. The responsibility rests with the deans of our medical schools, the physicians and surgeons in the teaching hospitals, the senior practitioners, for in their hands is the training of each oncoming generation by example rather than by precept, and any failure must lie with them. Medical ethics surely are primarily for the protection of the patients. Anything which harms them or lowers our status in their eyes is unethical. The examples you have quoted are surely infinitely small compared with talk about withdrawing from the N.H.S. I can think nothing more unethical than for any doctor to contemplate such action, with its implication that for extra gain ordinary people will be deprived of our assistance when they need it. Television medicine could do much good, though it should be regulated and some action is urgent. But since on grounds of ethics television doctors are to remain anonymous, so ought the physicians, surgeons, and accoucheurs to royalty and the famous; yet for generations they have failed to set the example we might reasonably expect, and indeed have advertised themselves in droves whenever opportunity offered.—I am, etc.,

Shipton under Wychwood, Oxford. GORDON SCOTT.

SIR,—Your leading article (*Journal*, May 2, p. 1170) suggests that in some way doctors connive at publicity, and even, at times, co-operate with it. I feel certain that in the majority of cases this is the reverse of the truth. I am equally certain that the nexus of the problem lies in the *Paris-Match* editorial reply to Professor Mathé, when they said in effect that his work was too important to remain anonymous, and in the statement of the president of our own National Union of Journalists that "in the mad race for newspaper

circulation, sensationalism ranks higher than service to the public."

I would have thought, in fact, that the thing to disturb us is not so much the attitude of the medical profession, which I feel basically remains the same as it always did, but the very changed and aggressive attitude of the national press. After all, it is only a few years ago since Professor Ian Aird, of the Postgraduate Medical School of London, gave us a succinct description of the fantastic happenings which occur when the press want a story and have some opposition in getting it (*Journal*, January 16, 1954, p. 153).

The public has a voracious appetite for medical knowledge, particularly of a sensational sort. The newspapers are determined that not only will this appetite be met but satiated. Their methods are ruthless, extreme, and never ending. Recently some work which I personally was trying to carry out in this hospital was seized upon by the press and blown up into a sensational banner headline about space travel. This was sufficient to bring down upon our heads a horde of reporters and photographers. In the following few days I repeatedly, energetically, and clearly requested them, and in two cases their sub-editors and others connected with the newspapers, not to use my name either in fact or by implication. All repeatedly, energetically, and clearly, with impeccable manners, promised that my name would never be used. The very next issue of the papers not only repeatedly used my name, but in one case a photograph of myself taken without my permission and indeed without my knowledge. At the height of this nonsense I was asked by the television authorities to appear and to "talk about this interesting work." On the advice of the senior administrative medical officer of the regional board I did so, mainly to dispel the fantastic ideas that a mental hospital was working on space-travel problems. In the actual studio I told the producer that if my name was mentioned I should immediately remove myself from the camera in the studio. This manœuvre was completely successful, and was the first occasion in the whole regrettable affair when I held the whip hand. I know of other colleagues who have experienced similar episodes, and I assure you, Sir, that we would go to any lengths to avoid such publicity again, which I may say gives any work that one might be doing an aroma of charlatanism and theatricality, the last thing, of course, that one wants to happen.

My experiences leave me in no doubt that the only way to deal with newspapers is to refuse categorically to see a newspaper man or else to hand out an approved statement of fact without interview. This statement should have been thoroughly vetted by one's hospital management committee and regional board medical authorities beforehand, and preferably also by as many other colleagues as one can possibly bring into it.

I am sure that most of our profession would wish for discretion, decorum, and anonymity. In these days, however, I submit that such pious sentiments by themselves are meaningless, and are completely ignored by the modern, tough, aggressive newspaper man, who, if he smells a story or something that could possibly be made into a story, will go and get it by hook or by crook, always pleading that "it is too important for the public not to know about it."—I am, etc.,

Lancaster Moor Hospital, Lancaster. S. SMITH.

SIR,—Nearly 60 years ago in my last year as a student at Glasgow a professor in his final lecture said: "In a short time a number of you gentlemen will be leaving here to enter practice. At some time you may desire to write a letter to the lay press. By all means write it, then place it in your desk overnight. In the morning read it, then tear it into fragments, and burn it."—I am, etc.,

Manchester, 21. G. H. GRANT DAVIE.

Top Surgeons

SIR,—Your editorial department is difficult to follow. You begin in the up-to-date style "Top Surgeons" (*Journal*, April 25, p. 1100), then get back to the old dull habit. You do not state which Sunday newspaper gave its readers a photograph of our surgical stars, so we cannot order a copy. This photograph should, of course, have appeared in the *Journal*.

Recently the B.M.A. shocked a nation with its "Getting Married" effort. Now it is itself shocked when some of our leading lights are being given publicity in the same way as the stars of the screen, stage, and sport. And why not? We live in a fast-moving, changing world. Our people should see and hear more about our great men. Why keep it a secret? We have, in my view, been far too "stuffy" in the past in our public relations, and the great names of medicine and surgery have been unknown even to the doctors of the period. The world should know more about us. We should be more human and less anonymous.

Advertising is another matter. Our leading men do not need to advertise, especially now that there are few people rich enough to become customers.—I am, etc.,

Shrewsbury ALBERT E. NICHOLLS.

*** The newspaper in question was the *Sunday Times*. If Dr. Nicholls wants to see more photographs of "top surgeons" he should borrow or buy *The Tatler and Bystander* of April 22.—ED., *B.M.J.*

Medicine on Television

SIR,—Although born sufficiently long ago to remember something of what life was like during the reign of good Queen Victoria, I pride myself on having become sufficiently attuned to the atmosphere of modern times to realize that the television screen has now taken the place formerly occupied by the altar, with the result that any criticism of a television programme has become more or less equivalent to sacrilege. I have also managed to assimilate the principles of the scientific age sufficiently to appreciate that nothing is any longer sacred except the television screen, and that the television camera has now replaced God as the agency from which, as the English Prayer Book used to say, "no secrets are hid."

It is, of course, in accordance with the principles in question that surgical operations should have been presented to the viewer on the television screen, and that interviews with patients should have been televised in apparent violation of the Hippocratic Oath which imposes an obligation of professional secrecy upon practitioners of medicine. Such recent television programmes as those concerning "The Birth of a Baby" and "Abortion" are equally in accordance with modern principles. It is to be hoped that these programmes will be repeated, as I know one boy aged 15 (and there are doubtless others) whose viewing of these programmes was, by a strange coincidence, interrupted by attacks of vomiting.

But why stop there? Surely it is almost an obligation to those who have enjoyed the programme on "The Birth of a Baby" to provide them with a complementary programme on "The Conception of a Baby." I know quite a number of 5-year-olds who are all agog to satisfy their scientific curiosity on this subject, and would welcome a visual demonstration (in the interests of

scientific knowledge) of what goes on between Daddy and Mummy during the hours of darkness. Nor should those who have taken a scientific interest in the subject of the Wolfenden Report be neglected. Indeed, this subject is at present so much in the focus of public attention and has so many facets that a whole series of programmes might appropriately be devoted to it on the television screen—with, of course, a final programme specially devoted to sodomy and all its refinements. Admittedly this programme might run the risk of offending that large body of public opinion which reflects the susceptibilities of the female prostitute—an individual whose relations with consenting males would appear, as the result of the Report, to have attracted some of the odium previously attached to the relations of one consenting male with another (this too in a civilization which prides itself on the equality of the sexes !). The practice of bestiality might well form the subject of another interesting programme, and other suitable subjects of a similar nature readily spring to the imagination. . . .—I am, etc.,

Edinburgh, 15. W. RONALD D. FAIRBAIRN.

Intermittent Suxamethonium Injections

SIR,—Dr. J. Bullough's observations (*Journal*, March 21, p. 786) regarding bradycardia and arrhythmia following injections of suxamethonium are of particular interest to me, as I am familiar with the sequence he describes but associate it with stimulation of the sacral autonomic system.

Whenever I observe a sustained fall in blood pressure with bradycardia in these circumstances, I restore the pressure by giving atropine—frequently the fall in pressure is so fleeting it appears to restore itself when the oxygen concentration is increased, which I think should be an automatic reaction to any sudden fall in blood pressure. The fact that Dr. Bullough notes that it occurs more commonly in females, in whom pelvic operations are more common, and that the case he describes is a vaginal operation, makes me wonder whether the syndrome is confined to sacral autonomic stimulation, as I do not think I can recall such a sequence of events during an upper abdominal operation.—I am, etc.,

Lethbridge, Alberta, Canada. J. SHEGOG RUDDELL.

Emotional Disturbances of Burned Children

SIR,—We read with great interest Miss Joan Woodward's article (*Journal*, April 18, p. 1009) on the emotional disturbances which follow thermal injuries to children. In this hospital, which admits over 200 burned and scalded children annually, we also have been concerned with this problem, but we are of the opinion that a major factor in its causation is physical pain.

During the last year we have been carrying out nearly all burns dressings under a general anaesthetic, and we believe that the incidence of emotional upsets in our patients has thereby been considerably reduced. This method is undoubtedly time-consuming for the surgical, anaesthetic, and theatre staffs, but we have found that, in addition to the improvement in the child's morale, the dressing can be carried out much more efficiently and satisfactorily and that the percentage of graft "takes" has increased. Interference with the patient's nutrition is reduced to a minimum by the employment of an anaesthetic technique which permits an immediate recovery to full consciousness. We have used a sleep dose of sodium thiopentone (4 mg./kg.), succinylcholine chloride, endotracheal intubation, nitrous oxide/oxygen, and hyperventilation. Sedation alone has, in our experience, proved quite inadequate for burns dressings unless carried to a stage of dangerous depression, persisting long after the dressing has been completed.—We are, etc.,

A. V. FORAGE.
J. H. JOHNSTON.
A. L. STEAD.

Alder Hey Children's Hospital, Liverpool.

Live Poliomyelitis Vaccine

SIR,—In the article on the "Present Position of Immunization Against Poliomyelitis with Live Virus Vaccines" (*Journal*, March 14, p. 663), Professor A. B. Sabin refers several times to experiments with two attenuated strains of poliovirus (Chat type I and Fox type III) developed by me. The purpose of this letter is to take issue with the results reported by Sabin, and in particular with respect to his allegation of the non-reproducibility of our results.

On page 678 Sabin states that tests of the Chat strain in his laboratory revealed the presence of "an unidentified, non-poliomyelitis cytopathogenic virus" in the pool. He had made a similar report to me in May, 1958, after he had tested the attenuated Fox III virus obtained from our laboratory, but no further elucidation has come from him—the inference one is left with is that further studies had disclosed it to be the same type III poliovirus which "broke" through the neutralization test in the lower dilutions. Two laboratories, apart from our own, have performed identity tests on the large Chat pool mentioned by Sabin with rabbit immune homotypic sera, and have failed to discover another "agent." It was impossible to make a direct check on Sabin's results because he failed to forward his "especially potent polio virus rabbit antisera" to our laboratory. Similarly, the "cerebral and spinal neurotropism" of his attenuated strains could not be determined because, once Sabin had our strains in his hands, he did not make his type I and type III strains available, although definite arrangements had been made for exchange of all attenuated strains between our two laboratories.

On page 667 Sabin refers to Chat type I and Fox type III strains of attenuated poliovirus as being "more neurotropic strains . . . [which] in the range of 10^2 and 10^3 TCD_{50} can produce paralysis." This claim is based on the results he obtained from intraspinal inoculation of monkeys with the two strains, shown in the Table on page 666. In this Table, Sabin gives a breakdown of the extent of involvement for his own material but neglects to do the same for the other samples tested, except to mention in the text that "with few exceptions" the paralysis which developed subsequently was extensive.

In Tables I and II I have summarized results of tests conducted in five different laboratories with samples from the same pool of Chat type I virus that Sabin employed for his study. In Table II the results of the five laboratories have been combined and are shown alongside the figures given in Sabin's table. Comparison of these two Tables indicates that our results are reproducible in other laboratories. Two contradictory inferences become apparent from examination of these results: either the research workers in the five laboratories do know how to inject monkeys intraspinally and intracerebrally and therefore Sabin's results are unexplainable, or Sabin's technique is much more refined than theirs and is the only one that is reliable. The latter view is belaboured in his article, and the results obtained by ourselves, Verlinde, and others are explained on the basis "of placing the inoculum too low in the spinal cord" (p. 667). The logic of this argument appears doubtful when one considers his statement, made in the course of a discussion of "cerebral" neurotropism (p. 663), that, when strains with exclusively "spinal" neurotropism are injected intracerebrally in a

manner to cause "a sufficiently extensive traumatic lesion to lay open the tracts leading directly to the spinal cord, enough virus can invade *the spinal neurones* [italics mine] without the necessary preliminary multiplication in the susceptible cerebral neurones." If a strain is capable of passing from the midbrain to the lumbar spinal cord, why does Sabin ask us to believe that the same strain encounters insurmountable obstacles that prevent its passage from the cord in the area of the third space above the iliac crest to the adjacent area of the fourth space? Nor is it clear then what he means by the importance of the actual site of inoculation when he states, as on page 667, "that inocula in the range of 10^3 and 10^2 TCD_{50} can produce paralysis despite the fact that the entire inoculum does not remain at the inoculated site by my procedure of spinal inoculation."

Another interesting aspect of the intraspinal inoculation of the Chat virus performed in Sabin's laboratory is revealed by the statement in Sabin's report to us that all but one of the monkeys developed paralysis within two to four days after inoculation and in none was paralysis progressive. Signs and symptoms have not been observed in our laboratory within a period of 48–96 hours after intraspinal inoculation of 100 TCD_{50} of virus.

That neither the area of effectiveness is so confined, nor that it plays so great a role as stressed by Sabin, but rather that the technique of actual injection into the cord is of importance, is evidenced by the results of tests performed by Melnick[1] with Sabin's own attenuated strains. Although Sabin states (p. 667) that "Melnick obtained a much higher incidence of paralytic manifestations than I did by my method," he does not say explicitly that, if the results obtained by Melnick with L Sc and P712 strains had been included in his Table I, the paralytic ratio of monkeys inoculated with his material would be directly comparable to that obtained with the "Brunhilde-Enders" strain—that is, a high paralytic ratio accompanied by extensive lesions in the spinal cord. Furthermore, one of Sabin's strains showed some "cerebral neurotropism" when tested even in diluted form.

In the light of Melnick's results and despite Sabin's claim (p. 679), the L Sc and P712 viruses *do not fulfil* the specifications laid down by the Expert Committee of the World Health Organization (July, 1957, session) for strains to be used in mass field trials, such as described in Sabin's article.

The above discussion should not be construed as an argument for the abandonment of trials, for large-scale field trials are the only effective means of evaluating the safety of attenuated virus vaccines. However, the principal guide in the selection of strains should be their characterization by all available "markers," and should not be influenced by the personal "trademark" they may bear.—I am, etc.,

H. KOPROWSKI.

The Wistar Institute of Anatomy and Biology, Philadelphia, 4, Pennsylvania.

TABLE I.—*Effectiveness and Reproducibility of Described Procedure for Comparing (in Five Different Laboratories) Spinal and Cerebral Neurotropism of (the Chat Koprowski) Attenuated Poliovirus in Monkeys*

Investigator	Laboratory	Species	Route	TCD_{50} Inoc. Log_{10}	Paralytic Ratio	Histological Lesions Ratio
De Somer	Virology, Univ. of Louvain	Rhesus	i.c.	7·3	0/12	0/6
		Cyno.	,,	7·3	0/12	0/12
		Rhesus	i.s.	7·0*	1/12	3/12†
		Cyno.	,,	7·0*	4/21	8/21†
Przesmycki	Polish State Institute of Hygiene, Warsaw	Cyno.	i.c.	7·5	0/12	0/12
	,,	,,	i.s.	6·5	4/12	4/12
Gard ..	Virology, Karolinska Inst., Stockholm	Cyno.	i.c.	6·0	0/4	1/4
Wyeth Lab.	Marietta, Pa.	Rhesus	i.s.	6·5	1/10	3/10
	,,	,,	,,	5·5	0/10	0/10
Koprowski and Norton	Wistar Institute, Philadelphia	Rhesus	i.c.	7·5	0/5	0/3
	,,	,,	i.s.	6·5	0/4	0/4
	,,	,,	,,	5·5	0/4	0/3
Grand Total			*i.c.*		*0/45*	*1/37*
			i.s.		*10/73*	*18/72*

Numerator = number of monkeys showing paralysis or histologic lesions; denominator = number of monkeys inoculated or submitted to histologic examination.

All monkeys received total of 1·0 ml. by intracerebral route given bilaterally in 0·5-ml. amounts; intraspinal inoculum consisted of 0·1 ml. except in cases marked by *, when the inoculum was 0·5 ml.

† 2 of rhesus and 4 of cynomolgus monkeys with minor lesions located at point of injection.

TABLE II.—*Direct Comparison of Intraspinal Inoculations*

TCD_{50} Inoc. Log_{10}	Sabin		Others	
	Paralysis	Lesions	Paralysis	Lesions
7·0–7·4	9/10		5/33	11/33†
6·2–6·5	5/5	Not reported	5/26	7/26
5·2–5·5	5/5		0/14	0/13
4·2	4/5			
3·2	4/5			
Titre*	>5·0		<1·0	

*50% paralytic or infectious end point calculated for 1 ml. of undiluted material.

† 2 of rhesus and 4 of cynomolgus monkeys with minor lesions located at point of injection.

REFERENCE

1 Melnick, J. L., *Proc. Soc. exp. Biol. Med.*, in press.

Catching up with Cabot

SIR,—I agree with your correspondents from McGill (*Journal*, May 16, p. 1304) that there is some merit in publishing clinico-pathological conferences as completely "blind" guessing games. Even in the Cabot cases, however, it is open to the reader to glance at the dénouement before he begins to read the story and with this knowledge he appreciates the perplexity of the diagnostician in trying to reach his conclusions. The title at the beginning ensures that the material is indexed in the medical literature and the investigative effort is not wholly lost.

All our clinico-pathological conferences are in fact presented with strict attention to the clinical problem and with an exact statement of how the clinicians reached their conclusions. The pathological data are only revealed *after* the clinician has made his statement. Often the case with easy diagnostic labelling contains detail of interest or even surprise.

There are several ways in which clinico-pathological conferences can be used in teaching: (1) A complex and often rather unique conglomeration of clinical phenomena may be presented. For example, the interrelation of disseminated lupus and malignant hypertension in the same patient is a matter worthy of consideration, although the diagnoses may be easy and obvious. (2) A case may be shown where the clinician grasped that there was some special or unusual feature, the solution of which was baffling. It is often better in these circumstances to have the case presented by the physician actually in charge of the patient, as it is only he who can give proper emphasis to the clinically puzzling features. (3) An invited expert may be asked to discuss "blind" a problem within the orbit of his special interest: his own special mode of approach makes a valuable lesson. After 20 years of attendance at these conferences I think I learn most from the analyses of some common disorder such as death from "chronic bronchitis." At least I can begin to appreciate the immensity of the unsolved problems that still face us.—I am, etc.,

JOHN MCMICHAEL.

Postgraduate Medical School, London, W.12.

Serum Gonadotrophin in Acne

SIR,—I should like to reply to Dr. Lipman Cohen's letter on the use of serum gonadotrophin in acne vulgaris (*Journal*, March 14, p. 715). I am of course aware that serum gonadotrophin should be absorbed through the buccal mucosa, and I endeavoured, in the course of the trial I described (*Journal*, February 28, p. 557), to ascertain that this was done by the patients—several of whom complained that the tablets stayed in the mouth much longer than two hours. I cannot therefore accept this explanation of my results. Although I am sure Dr. Lipman Cohen does not simply ascribe his failures to an inability to use the treatment properly, I hope he does not unquestioningly attribute his successes to such an ability. I remain unconvinced of the value of this treatment and await with interest his publication of a controlled investigation.—I am, etc.,

Department of Dermatology, University of Tabriz. JOHN H. S. PETTIT.

Phenylbutazone and its Derivatives

SIR,—We were interested to read the report by Drs. F. Dudley Hart and Denis Burley (*Journal*, April 25, p. 1087) on the use of the phenylbutazone derivative G.27202, and we would like to record our own observations on this drug. A small pilot trial was carried out in this department, in which 25 patients who were unable to tolerate phenylbutazone for various reasons were given G.27202. The drug was administered in 100-mg. tablets, the usual dosage being 300 mg. per day for one month. Our results were as follows:

No. of Patients with Different Toxic Reactions to Phenylbutazone	No. of Patients	
	Able to Tolerate G.27202	Unable to Tolerate G.27202
Dyspepsia and nausea .. 12	8	4
Stomatitis (including sore throat and tongue, and buccal ulceration) .. 9	6	3
Rash 3	2	1
Oedema 1	0	1 (Tolerated well for 2 months before oedema recurred)
Diarrhoea 1	1 (With slight diarrhoea)	0
Vertigo 1	1	0

The total number of patients intolerant to phenylbutazone was 25; of these 18 (67%) were tolerant to G.27202. The patients were suffering from the following conditions: rheumatoid arthritis 12, ankylosing spondylitis 9, osteoarthritis 3, and low back-pain (undiagnosed) 1. Two patients developed more than one symptom of intolerance to phenylbutazone.

We therefore can agree with Drs. Dudley Hart and Burley that G.27202 seems to be a drug of value in the treatment of patients intolerant to phenylbutazone. Our clinical impression was that G.27202 was a less powerful analgesic agent than phenylbutazone, but only slightly so. In six cases, all developing stomatitis with phenylbutazone, there was no abnormality in the white cell count after treatment with G.27202, or after stopping the drug because of recurrence. Three patients who had severe buccal ulceration with phenylbutazone produced buccal ulcers of similar severity with G.27202. We feel that G.27202 should be used with great caution in this type of patient.

It must be stressed that, although the toxicity of G.27202 in both trials seems to be less than that of phenylbutazone, the drug has, as yet, been tested over a short period. In some of the patients in this trial intolerance of phenylbutazone did not develop until they had been taking the drug for up to four years. It does seem from the studies to date that G.27202 is a drug of considerable value in painful locomotor disease and that there is a need for long-term observation of its toxicity and clinical effects. Our experience tallies with that of Drs. Dudley Hart and Burley, that ankylosing spondylitis patients are the best and most consistent observers of the analgesic effect of this type of drug. They could make accurate comparisons of analgesic effect of phenylbutazone and G.27202 and could state an exact time of cessation or lessening of pain after taking either drug. Is this because the age group was lower than patients with other conditions participating in the trial, or because the effect of this type of drug is almost specific for the pain in this condition?

Our thanks are due to Dr. W. S. Tegner for permission to use clinical material in the department, and to Dr. W. S. Stoddart, of Geigy Pharmaceuticals Ltd., for supplies of the drug.

—We are, etc.,

R. M. MASON.
FRANK CRAMER.

Department of Physical Medicine and Regional Rheumatism Centre, The London Hospital, London, E.1.

Vulval Varicosities in Pregnancy

SIR,—Mr. Harold Dodd and Dr. H. Payling Wright (*Journal*, March 28, p. 831) have drawn attention to a not uncommon complication of pregnancy which has received relatively little attention in textbooks and literature. It would be the more regrettable, therefore, if readers were to believe that surgical interference during pregnancy was the treatment of choice. For most patients this is a temporary, though at times distressing, complication with a surprising return to a more normal state early in the puerperium. Tight-fitting pants of elastic material applied when the patient first gets up in the morning reduce the need for surgical interference to the very exceptional case.

Occasionally a localized condition resembling a cavernous haemangioma can develop anywhere on the vulva, even round the urethral meatus. It regresses in the puerperium as rapidly as it developed during pregnancy, and any discomfort can be controlled by the simple support referred to above.—I am, etc.,

The Radcliffe Infirmary, Oxford. JOHN STALLWORTHY.

SIR,—I have read with interest recent correspondence by Mr. R. Rowden Foote and Dr. A. Koby (*Journal*, May 2, p. 1185) concerning the treatment of varicose veins in pregnancy. As regards vulval varices in particular, I have obtained relief from symptoms with the injection of 3 ml. of ethanolamine. At the same time it must be observed that many patients with vulval varices do not experience any discomfort from them. I agree with Mr. Rowden Foote that operations in this region during pregnancy are fraught with danger and should be avoided.—I am, etc.,

St. Asaph, N. Wales. A. H. HOLMES.

Reappraisal of Thymectomy

SIR,—I hasten to reassure Dr. H. Windsley (*Journal*, March 14, p. 717) that at this unit we are constantly exercising our minds about this mysterious and as yet inexplicable disease—myasthenia gravis. However many thoughts he might suggest about thymectomy, our figures support the contention that in our present state of knowledge thymectomy still offers the best hope to these unfortunate sufferers.

In a current review of thymectomies undertaken at this unit since 1942 (over 150 non-tumour cases) the overall mortality, including operative deaths, was found to be 20%. Forty patients had dispensed with the cholinergic drugs years ago and were doing a full and normal day's work. Furthermore, in this group of patients the average "remission" time was found to be 7.5 years. Osserman in a review of 310 cases treated medically claims an average remission period of 2.8 years.[1]—I am, etc.,

M. J. LANGE.

New End Hospital,
London, N.W.3.

REFERENCE

[1] Osserman, K. E., *Klin. Wschr.*, 1959, **37**, 7.

Telling the Cancer Patient

SIR,—The correspondence arising from the article by Miss Jean Aitken-Swan and Dr. E. C. Easson (*Journal*, March 21, p. 779) has been very interesting, and surely should make us all think. It has certainly set me thinking over the last 27 years.

I have known many cancer patients. Most of them have never known of their complaint and lived fairly comfortable until finally stricken. A few, however, have known they had cancer, often by badgering a specialist or from a well-meaning house-surgeon or nurse. No doubt they received the news with courage—even a "Thank you, Doctor, for telling me," but what about later? I can honestly say I have not met anyone who has received his death knell and been the same person again. There has always been a sadness, joylessness, and hopelessness left. Often a neurosis develops, and a trifling complaint means their "cancer" is returning.

I remember, especially, a lady who insisted on the truth. She had an advanced carcinoma of the cervix, and should not be alive to-day. She heard her death warrant in hospital and on leaving proceeded to spend a small inheritance on her friends. I received a beautiful piece of Dresden china which I much value. But death did not come as she thought, and that is four years ago. Having spent her all on death-bed presents she is now compelled to work full-time—but I must admit she is enjoying it, and is very well. She has often said to me, "If only I had never known"; no doubt she would be just as well, and have her little inheritance to boot.

You know, Sir, doctors should never be judges, never put on the black cap, or gain self-importance by speaking precipitately. We should remember, "You never regret what you don't say"—and remember that the family doctor, the one who really knows his patient, should be the one with the final decision on whether to tell the patient or not. I would hazard his decision would be wise and humane.—I am, etc.,

HILDA SWINBURNE-JONES.

Blackpool.

Prophylactic Tetanus Toxoid

SIR,—Mr. R. Pitts Crick (*Journal*, May 2, p. 1187) advocates active immunization with tetanus toxoid, thus avoiding anaphylactic reactions in patients who have prophylactic antitetanus serum.

Another aspect of this matter has always worried me. When one reads the makers' instructions which are enclosed with each ampoule of antitoxin we are told that all cases where the serum has been administered must be kept under observation for 30 minutes. If trouble is anticipated (e.g., in patients who have had serum before) a test dose is given and the remainder after 30 minutes (60 minutes altogether). In cases of asthma or allergic eczema, a diluted dose is given followed by a small dose in 30 minutes. The main dose is given 30 minutes later and the patient kept under observation for another 30 minutes (90 minutes altogether).

The purpose of this letter is to remind colleagues that the recommendations exist. In my opinion a coroner would have little sympathy with a doctor who did not follow the instructions. I would like to see an authoritative body (such as the Medical Research Council) giving definite instructions covering the whole immunization programme.—I am, etc.,

JOHN H. HUGHES.

Aberystwyth.

Vaccination Against Whooping-cough

SIR,—The Final Report to the Whooping-cough Immunization Committee of the Medical Research Council (*Journal*, April 18, p. 994) mentions 15 cases of convulsions following pertussis immunization, six of which occurred within 72 hours of injection. We should be interested to know if any of these children were observed to have neurological sequelae. Recently we reported (*Journal*, July 26, 1958, p. 246) 6 cases of convulsions after pertussis immunization, one fatal and three followed by evidence of lasting brain damage. Would it not be advisable to emphasize that convulsions and other neurological complications are especially liable to occur in children with a previous history of convulsions or in whom there was a reaction after the first dose?—We are, etc.,

D. C. THURSBY-PELHAM.
C. GILES.

City General Hospital,
Newcastle Road,
Stoke-on-Trent.

The Late Dr. Crichton-Miller

SIR,—I have been asked by the family of the late Dr. Hugh Crichton-Miller, psychotherapist and founder of the Tavistock Clinic, to write his life. I should be grateful if any of your readers who have any letters from him, or information about him, would get in touch with me at The Vineyards, Beaulieu, Hants.—I am, etc.,

R. F. GORE BROWNE.

Hazards of Ship Surgeons

SIR,—Permit me to congratulate you on the medico-legal article, "Hazards of Ship Surgeons" (*Journal*, April 18, p. 1051).

Complementary to the medical defence coverage recommended in that excellent article, I would like to suggest that it is essential for the ship surgeons of to-day to exercise the utmost care in seeing that precise and accurate notes are entered in the medical log books concerning all examinations, operations, and therapeutic measures carried out at sea by members of the ship's medical department.—I am, etc,

P. WALSHE,
Ship Surgeon.

London S.W.7

POINTS FROM LETTERS

Psychosomatic Disorders in Children

Mr. K. W. MONSARRAT (Farringdon, Berks) writes: May I express agreement with Dr. Lindsey W. Batten's remarks in his article on psychosomatic disorders in children (*Journal*, April 25, p. 1109) on the use of the hybrid word psychosomatic? . . . If a word is required to signify the participation of the nervous system and other systems (in sum somatic) in particular human disorders the appropriate adjective is neurosomatic.

Obituary

A. I. SHEPHEARD-WALWYN, M.D., F.R.C.P.Ed.

Dr. A. I. Shepheard-Walwyn, honorary consulting physician to the Cumberland Infirmary, died at Aglionby, near Carlisle, on April 6 at the age of 77.

Alfred Irving Shepheard-Walwyn was born at Windermere on October 29, 1881, and was educated at Rugby School and Edinburgh University, where he graduated M.B., Ch.B. in 1905, proceeding to the M.D. four years later. After graduation he held the appointments of clinical assistant, house-physician, and house-surgeon at Edinburgh Royal Infirmary and house-physician at Paddington Green Children's Hospital before he settled in practice at Wetherall, Cumberland. Later he moved to Carlisle and became physician to the Cumberland Infirmary. He was elected a Fellow of the Royal College of Physicians of Edinburgh in 1926.

J. N. J. H. and J. A. R. write: Though Shepheard-Walwyn retired in 1946 and, partly because of indisposition, took little active part thereafterwards in medical affairs, he will still long be remembered by the many practitioners in Cumberland and neighbouring counties in the north-west of England and over the Scottish border for his valuable service as a medical consultant. As an undergraduate in Edinburgh Shepheard-Walwyn sat at the feet of distinguished teachers—Crum Brown, William Turner, and Schafer, and among the physicians, Byrom Bramwell, Robert Philip, Thomas R. Fraser, George Gibson, Greenfield, and many others. He became house-physician to George Gibson, a pioneer in cardiology, with whom he retained a lifelong friendship. Later he studied for a time under Parkinson in London, and naturally acquired a special interest in cardiology. But Shepheard-Walwyn, having a wide experience of many branches of medicine, was essentially a general medical consultant.

As honorary members of the Cumberland Infirmary staff we were closely associated with Shepheard-Walwyn, one of us for a period of nearly three decades and the other for two, and both were privileged to become his intimate friends. As a medical consultant he possessed outstanding qualities. His examination of a patient was meticulous and comprehensive, he kept pace with advances in medicine and made use of various laboratory techniques as soon as their value was established. He had a high sense of medical responsibility and spared no time or effort when presented with a clinical problem. His long and wide experience gave him an uncanny intuitive faculty in diagnosis, but his final opinions were invariably based on a careful and logical consideration of all the data obtained: and how wise these opinions were.

Hospital duties and private work left him little spare time for recreation when in Carlisle. He had, however, many hobbies, in all of which he excelled. He came of a musical family and was himself a skilled pianist. Of his other hobbies the chief were fishing, shooting, photography, and gardening. Some of the happiest memories we shall retain of him are of the occasional stolen day spent with him and his spaniels walking up partridge in the turnip field, or of shooting driven grouse on the Pennines, or of a day fishing on the Eden or one of its tributaries. He rarely travelled abroad, but for holidays sped immediately north to his beloved Scottish lochs and rivers. His favourite haunt was a small, unpretentious but comfortable inn on the banks of Loch Awe. After retiring, and especially when he became less vigorous, Loch Awe was his favourite retreat, and he and a number of his friends usually forgathered there in spring and autumn. He retained a boyish spirit to the end, and those who were fortunate enough to share these holidays will have a wealth of memories of fishing on the loch, of picnics on its shores and islands during the day, and of happy evenings spent by a log fire. It is beside this loch, at his request, that his ashes have been scattered. Our sympathy goes out to his widow, who, though much disabled by rheumatism, nursed her husband with such devotion and skill during his last distressing illness. Our sympathy is also extended to their two sons, both graduates of Edinburgh University, one a schoolmaster in the south of England and the other a lecturer in a school of agriculture in New Zealand.

JAMES KELMAN, M.D., D.P.H.

Dr. James Kelman, medical officer of health for the counties of Perth and Kinross since 1946, died at Perth Royal Infirmary on April 24. He was 56 years of age.

A native of Keith, Banffshire, James Kelman was born on November 9, 1902, and was educated in Dundee. He graduated M.B., Ch.B. at St. Andrews University in 1926, took the D.P. in 1930, and proceeded M.D. in 1939. After acting as house-physician and house-surgeon at Dundee Royal Infirmary he was resident medical officer at Noranside Sanatorium, in Angus, from 1928 to 1931. Appointed assistant medical officer of health for Angus in 1931, he became assistant medical officer of health for Perth and Kinross a year later, succeeding to the senior post in 1946. He gave valuable help on medical and welfare committees in the city and county, and his B.C.G. scheme was one of the first in Scotland.

Dr. Kelman was honorary secretary of the Perth Branch of the British Medical Association from 1941 until his death, and had been honorary secretary of the local medical committee since the institution of the National Health Service. In these capacities he became well known to all doctors in the area, especially to those in general practice. He was a constant source of help and encouragement and gained their great respect and affection. He served on several committees of the B.M.A., including the Scottish Committee (now Council) since 1948, the Public Health Committee since 1951, the Constitution Committee, and the Royal Commission Evidence Subcommittee (public health). He was a member of the council of the Sanitary Association of Scotland, and at the time of his death president-elect of the Scottish branch of the Society of Medical Officers of Health.

Music provided one of the few reliefs he allowed himself from a life of dedicated service. As a student he travelled widely with a ship's band, and he was a member of the Perth Symphony Orchestra. He seemed well on the way to recovery from the illness which had struck him down six weeks previously, and was engaged in a discussion on the future activities of the Perth Branch of the B.M.A., for which he had done so much, when the end came suddenly and peacefully. He leaves a widow and a young daughter, to whom our deepest sympathy is extended.—J. S.

C. J. S. writes: James Kelman was quiet and unassuming in his manner but highly efficient in whatever he put his mind to. He was one of the most broad-minded of men in the public health service in Scotland. Although he had never actually engaged in general practice he had an intimate knowledge of the workings and a sympathetic appreciation of the problems of family doctoring, and this, coupled with his early experience in hospital, made his influence a potent factor in the closer interpretation of the three parts of the health service in Perthshire. As honorary secretary of the Perth Branch of the B.M.A. and of the local medical committee his work was beyond praise, and only now that he is gone can we in Perthshire fully realize how much time and thought and real hard work he must have given to those duties and how much we depended upon him for the smooth running of our committees. In the wider sphere as a member of the Scottish Council of the B.M.A. and of the Public Health Committees in both Edinburgh and London, his sound, practical common sense was much sought after and his contributions to the debates were highly appreciated and respected. Truly his passing is a great loss to the profession in Scotland, and in Perthshire there is a blank that will not readily be filled.

RUTH C. EASTERLING, M.R.C.S., L.R.C.P.

Dr. Ruth Easterling, who died at Welwyn Garden City on April 8 at the age of 73, was a historian of distinction before she qualified as a doctor 25 years ago.

Ruth Clark Easterling was born in London on August 2, 1885, and was educated at Cheltenham Ladies' College and at Bangor College in the University of Wales. She took an honours degree in history, and was awarded a research studentship in 1913, the second year of which was to be spent in London: this was later converted to a fellowship. In 1914 she began postgraduate work at the London School of Economics and published the result of this work, "Friars in Wales," in *Archaeologia Cambriensis*, and "Elnior, Bishop of St. Asaph" in the Flintshire Record Society's journal. After several years at the London School of Economics, she worked with Dr. Hubert Hall, Deputy Keeper of the Rolls, and in 1919 did research work on Sir Francis Pigott's staff. She then went to Exeter as a member of the staff of the Royal Albert Memorial College, which was about to be granted a charter as a university college. She was appointed to lecture in the honours course in history and to do research work, and it was at this time that she made the dramatic discovery of the importance of the Exeter Records.

In 1927 she began her medical career and entered King's College Hospital, qualifying M.R.C.S., L.R.C.P. in 1934. After holding several house appointments in London she returned to Exeter to be with her mother and took an assistantship in general practice. Always most interested in psychological medicine, she later acted as locum for long periods at the Digby Mental Hospital and Wonford House Hospital, Exeter. Her last work was to make a report on the records of the Royal Devon and Exeter Hospital and of Wonford House Hospital. For the last few years of her life her health was poor and she was in constant anxiety that the fruits of both her historical and psychological research should not be lost. Finally she was moved to the home of a devoted life-long friend in Welwyn Garden City, where she died.

Ruth Clark Easterling was a woman of complete integrity and was respected and loved by all who knew her. Unassuming and exceedingly modest, she was unfailingly kind and generous to her patients and deeply loyal to her friends. One of her oldest friends has written, "Ruth Easterling was one of those scholars who was deeply learned in her own subjects, and she had many. Nevertheless, in the ways of the world she was simple to a degree which excites cupidity in the dishonest and ignorant, but compassion and love in the friendly."—S. J. P. G.

Medical Notes in Parliament

RADIATION BY INSTALMENTS

The Prime Minister's considered statement on radiation hazards (*Journal*, May 9, p. 1248) has become, for the time being at any rate, the basis for a twice-weekly class. There is a hazard of its own about the lesson, because whether it begins early enough to be useful—or even at all—depends on the clock, which at least is a constant factor, and on the amount of time M.P.s spend on interrogating other Ministers first on almost every other subject. Questions to the Prime Minister begin, by long-standing custom, at No. 45, and as a matter of convenience are largely restricted to Tuesday and Thursday in each week. On the topics which engage other Ministers between questions 1 and 44 depends how much of the question hour is available for interrogation of the Prime Minister.

Where Does Most Come From?

Thus on May 5 there were eight questions awaiting Mr. MACMILLAN on radiation topics, of which only two were asked verbally, and two others received written answers. In the time he had Mr. Macmillan set out the proportions of radiation to which mankind was subject in this ratio: 100, existing natural radiation in the world, the inevitable, ineluctable radiation ever since creation; about 22, in the United Kingdom (more in the United States), from medical *x*-rays, various industrial processes, wrist watches, etc.; between 1 and 2, the result of nuclear fall-out.

One of the aspects that attracted much attention was the threshold dose, but the answer to that came more concisely in written form to a question that Dr. BARNET STROSS had put down about strontium-90. He was told that, while existing evidence did not permit a firm decision as to whether there is a threshold dose, there was no direct evidence that radiation from the minute amounts of strontium-90 in human bone had caused injury to anyone.

Fall-out on Britain

On May 7 six more questions appeared for oral answer. Three of them, which the Prime Minister took together as one group, dealt with the measurement of strontium-90 deposits in the United Kingdom and particular areas, and he explained the method by which the figures were reached, subsequently adding that it took about three months to complete a determination of strontium-90, and then there must be the interpretation of the results in relation to each other; to be of any value the results should cover a sufficiently long period to iron out temporary or short-term effects of unusual phenomena.

In his answer, Mr. MACMILLAN said that about half a dozen monitoring stations were established in different parts of the country (including one in Scotland), and at these the deposition of strontium-90 was measured in relation to the rainfall. It had been found that the amount of deposition of strontium-90 varied with the rainfall. It was therefore possible to estimate what amount of strontium-90 was likely to be deposited in any area in the United Kingdom for which the rainfall was known. In addition, samples were taken of strontium-90 in food (especially milk), herbage, and soil in many different areas, and these supplied complementary information. The figures were published from time to time. The maximum deposition of strontium-90 observed had been at two stations on Snowdon, both of which were at a high altitude. The latest Atomic Energy Authority report on this subject gave the figures for these two stations for the first six months of 1958 (8.3 and 9.6 millicuries of strontium-90 per square kilometre). These levels were some four to five times the representative value for the country as a whole. This reflected the higher rainfall of that area.

Mr. HUGH GAITSKELL, Leader of the Opposition, recalled the impression left by the earlier pronouncement that strontium deposits had doubled within a year, and questioned Mr. Macmillan about this. The PRIME MINISTER in reply summarized paras. 281 to 284 of the Medical Research Council's Report, and said that the concentration of strontium had not reached anything like the figure of 100 units which the M.R.C. had accepted for working purposes (compared with the 1,000 units accepted by the International Committee on Radiological Protection as a maximum permissible level for adults in special occupations).

Chances of Reducing our Exposure

Captain R. A. PILKINGTON (Poole, Con.) asked what measures had been taken to reduce nuclear radiation other than that caused by bomb tests. Mr. MACMILLAN said it was not possible to reduce radiation from the principal source to which mankind was exposed—namely, the natural background. As regards medical uses, Lord Adrian's Committee had just issued an interim report* which needed careful study. As regards industrial radiation, various measures had been taken. It was the policy of the Government that all operations involving the use of ionizing radiation should be carried out in such a way as to keep to a minimum the extent to which persons were exposed to such radiations.

*See *Journal*, May 9, p. 1232.

The replies which supplementary questions evoked from the Prime Minister included the statement "We must do our best to reduce what is within our power to reduce. What is within our power is this very large amount for medical uses, a considerable amount from industrial uses, and this amount from nuclear explosions. We should however keep them in proportion, although nobody is more anxious than I that the negotiations at Geneva should have the effect of taking out the last, although by no means the most important, of these three."

Mr. Macmillan also stated in answer to Captain PILKINGTON that the proportions—1, 22, and 100 of radiation from nuclear tests, other man-made radiation, and natural causes—might have been somewhat affected by the most recent tests, but the change would not amount to more than making the figure of one unit something between 1 and 2.

Least Radiation in Wooden Buildings

Another question related to the variations in natural radiation, and on this Mr. Macmillan said that radiation varied greatly in different parts of the world, and, curiously enough, according to the buildings in which people lived. In some parts of the world, quite apart from the effect of buildings, the natural radiation amounted to 10 times the normal world level. Apart from some small local variations the normal world level applied throughout the United Kingdom; we did not have the great extremes that some countries had. As regards buildings, natural radiation was normally lowest in wooden houses; the body dose in brick or concrete houses was about 25% higher than outdoors; and the dose was somewhat higher again in stone and especially granite houses.

A question from Dr. EDITH SUMMERSKILL (Warrington, Lab.) brought the information that so far there had been no direct evidence of any genetic effects on man from very low rates of radiation.

Effect on Bone Marrow

As things turned out there was an extra lesson too, for Mr. R. MOSS (Meriden, Lab.) and Mr. F. ALLAUN (Salford, East, Lab.) had put down several questions for written reply, all of a highly technical character, which were answered on May 11.

Mr. MOSS wanted to know the proportions of radiation derived from various sources affecting the mean marrow dose, assuming there were no more tests of nuclear devices; and to what extent the answer would differ in countries depending upon a plant-type diet.

Mr. MACMILLAN said he was advised that the average mean marrow dose of radiation from strontium-90 in the United Kingdom was at present less than 2% of that due to the natural background. The mean marrow dose of radiation from medical uses of *x*-rays was under consideration by the Adrian Committee and figures were not yet available. Comparable figures were not available from countries depending on a plant-type diet.

Strontium-89

Mr. ALLAUN asked for the figures of strontium-89 in fall-out now; and what proportions of the total radiation dose in bone the isotope was expected to account for.

Mr. MACMILLAN explained that the ratio of the dose to bone from strontium-89 as compared with that from strontium-90 depended, among other things, upon the ratio of the content of strontium-89 to strontium-90 in the diet at the time of ingestion and not on the relative content in the fall-out. The values for diet in the United Kingdom in 1958 would be published shortly. It was expected that the dose from strontium-89 would fall well within the range 1–20% quoted by the United Nations Committee. There was at present no reason to believe that the position would change significantly. The ratios of strontium-89 to strontium-90 in fall-out would be published from time to time as results became available.

Analyses in Young Children

Mr. ALLAUN stated in another question that only 27 analyses had been undertaken of the strontium-90 level in 1- to 5-years-old children, although the average level in children of 1 to 2 years and of children 2 to 3 years was higher than in other age groups. He wanted this research extended without delay. Mr. MACMILLAN said that over a hundred measurements of strontium-90 in the bones of children from 1 to 5 years old had been made in the United Kingdom, of which 27 were undertaken in the first three months of 1958. Every effort was being made, wherever possible, to increase the number of such analyses.

Radiation in Factories

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) asked the Minister of Labour on May 11 how many factories were using radioactive isotopes; how many operated *x*-ray apparatus among those using sealed sources of ionizing radiations; what was the approximate number of workers exposed; and the number receiving blood examinations at regular intervals.

Mr. RICHARD WOOD, the Parliamentary Secretary, informed him that there were at present some 560 factories using radioactive isotopes. Some 475 factories used sealed sources of radioactive substances, and some 260 factories used *x*-ray apparatus; there were cases where both were used, but he could not say how many. In all, there were some 3,000 persons employed in the processes, and two-thirds of these received blood examinations.

Dr. STROSS asked for a statement on the health, including the presence of changes in the blood count, of the woman employee, described in the report of the Chief Inspector, who was subjected for one week to working with grade 120 radium in 1956; whether she was still employed as a luminizer; and what treatment has been given.

Mr. WOOD stated that the woman had been regularly examined by the appointed factory doctor in accordance with the Luminizing Regulations. At the last such examination earlier this month she was recorded as being in a satisfactory state of health. In addition, she had been examined on several occasions by a medical inspector of factories in the course of routine haematological investigations of persons exposed to ionizing radiations. The most recent examination was in April this year when, both clinically and haematologically, nothing abnormal was found.

DISMISSED CONSULTANT

Another short debate, on May 12, on the case of Mr. A. H. Barber, the consultant who was dismissed from the service of the Manchester Regional Board in 1957, brought an indication from the Parliamentary Secretary to the Ministry of Health of the Ministry's intention to put "teeth" into the "moral obligation" commitment. Mr. C. L. HALE (Oldham, West, Lab.), who brought the subject up again, said he now felt the time had come when he should reveal the whole of this wicked secret trial and a wicked plot to slander a man that had gone on for year after year. Mr. Barber still did not know what had been alleged against him, in what way he had been "tactless," or what "errors of judgment" he had committed.

On the second application after his appeal to the courts he had been put on the short list for an appointment by four votes to three, and then a representative of the Manchester Regional Board had said that if he remained on the short list he would have to get the job because the Minister had said that there was a moral obligation in his favour. The committee had then taken a second vote and Mr. Barber was removed from the short list by four votes to three. This was a dark and malicious conspiracy supported by constant misstatement of fact, slander, malice, envy, and all uncharitableness—a conspiracy which, if a

severe view were taken, could be indictable at common law. What was certain was that this plot had ruined this man, had kept him out of employment, and was now depriving him of any chance of future employment unless the Minister took action.

New Regulations Promised

Mr. RICHARD THOMPSON, replying, said there was no doubt that Mr. Barber's appointment had originally been wrongfully terminated, but the High Court had negatived his claim that he was entitled as of right to re-employment by the board. Neither the court nor the Minister had the power to insist upon that. Nevertheless, the Manchester Regional Board had accepted the moral obligations. As a result of allegations made, inquiries had been made into the most recent decision of the appointments advisory committee, and it was not a fact that there was a change in the number of persons prepared to vote in favour of Mr. Barber as a result of a statement made by an officer of the board. At no time had there been a majority for submitting Mr. Barber's name.

The Minister intended to make new regulations which would strengthen the operation of the moral obligation commitment. They would not be compulsive but permissive. Nevertheless, they would ensure that the moral obligation would operate at the very outset, where any consultants were concerned, by removing the possibility of their being eliminated in the qualifying round before the moral obligation had had a chance to weigh in their favour. This would go a long way to meet the implied criticism that the whole purpose of the moral obligation might be frustrated. The Minister took a serious and continuing interest in this matter and was anxious that the moral obligation commitment should be, and should be seen to be, a reality.

BRITISH SATELLITE PROJECT

The promised statement on a British earth satellite (*Journal*, May 16, p. 1306), when it eventually came on May 12, wore much of an interim and preliminary air. What the Prime Minister had to say was this:

"There are two problems to be considered in relation to a British contribution to space research; the nature and design of the instruments to be carried into space; and the means by which the containers for these instruments are launched. With regard to the first, with the assistance of Fellows of the Royal Society and with the endorsement of the Advisory Council on Scientific Policy, a programme for the design and construction of instruments to be carried in earth satellites has been approved. Work will begin at once.

"With regard to the second, there may well be scope for joint action with the United States, with the Commonwealth, or with other countries. We therefore plan to send to Washington a team of experts, including Professor H. S. W. Massey, to discuss possible Anglo-American co-operation; and we are also opening consultations with other Commonwealth countries. Meanwhile, however, design studies are also being put in hand for the adaptation of the British military rockets which are now under development. This will put us in a position, should we decide to do so, to make an all-British effort.

"I have asked the Lord President of the Council, in consultation with the Minister of Supply and other Ministers concerned, to exercise general supervision of these new developments."

The subsequent interrogation added little to this.

QUESTIONS IN THE COMMONS

Protection Against Head Injury

Mr. Moss asked the Minister of Transport and Civil Aviation on May 6 whether he had noted that the causes of deaths in motor vehicle accidents in 1955 were head injuries as to nearly 66% in the case of pedestrians, over 77% in the case of pedal-cyclists, 80% in the case of riders or passengers of motor-cycles, and over 52% in the case of riders or passengers of other vehicles; and what steps he will take, within his existing statutory powers, to encourage the wearing of crash-helmets, the cushioning of cars, and the wearing of protective hats and caps.

Mr. G. R. H. NUGENT, Parliamentary Secretary, said he was aware of the head injury figures quoted. Proper protective helmets afforded a good degree of protection from head injury to motor-cyclists, and every opportunity was taken to encourage their use. It would be premature to recommend other protective hats or caps, or cushioning of cars, until more was known about the degree of protection afforded. He explained that the Road Research Laboratory and the motor manufacturers were doing research work to see what design for cushioning dashboards would be most beneficial. He resisted a suggestion by Sir GODFREY NICHOLSON (Farnham, Con.) that the wearing of crash-helmets should be made compulsory, saying that the voluntary campaigns had been effective and more than 50% of motor-cyclists now wore them.

"Slimming" Bread on I.T.V.

Dr. D. CHAPMAN (Birmingham, Northfield, Lab.) asked the Postmaster-General on May 6 whether he was aware that, despite its own rules forbidding advertisements which made medical claims from showing medical, nursing, or similar professional people as recommending their product, the Independent Television Authority was screening an advertisement for a particular form of bread recommended for slimming by such a person; and, as the Authority was failing to enforce its own rules in this way, whether he would make regulations under Section 4 (4) of the Television Act to prevent the showing of such advertisements.

Mr. KENNETH THOMPSON, Assistant Postmaster-General, said the rules referred to related to the advertising of medicines, treatments, and products which were claimed to promote health or to be beneficial in illness. The bread in question was not a medicine or treatment. The Authority was, however, already looking into the presentation of this type of advertisement.

Children's Eyesight and Television

Mr. D. WADE (Huddersfield, West, Lib.) on May 11 asked the Minister of Health what researches he had undertaken into the effects upon the eyes of children under the age of 15 years of watching television; what information he had thereby obtained; and what conclusions he had reached as to the harmful effects upon children's eyesight or otherwise on their health. Mr. WALKER-SMITH replied that existing medical knowledge was sufficient to conclude that no harmful effects upon children's eyesight might be expected to follow from watching television, nor was there any reason to apprehend that any harmful effect on health generally resulted from this pastime.

Salmonellae in Egg Products

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) asked the Minister of Health, in view of the widespread infection by salmonella organisms or paratyphoid B found in many types of processed eggs, whether imported or home produced, what action he was taking to ensure pasteurization of egg mixes before freezing.

Mr. R. THOMPSON, the Parliamentary Secretary, replied that all bulked egg products were liable to yield salmonella organisms. The commonest type, *Salmonella pullorum*, was regarded as non-pathogenic. *Salmonella paratyphi* B was not widespread. Some practical difficulties had still to be overcome before pasteurization of bulked egg on a commercial scale could be regarded as fully reliable. The Ministry of Health was considering what might usefully be done to encourage work already going on in the trade and elsewhere on ways of overcoming the difficulties. In the meantime, local authorities and port health authorities were regularly sampling egg products for infection with salmonellae and taking safeguarding measures where necessary.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 2** (No. 17) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	1	2	0	1	3	1	3	0	
Dysentery ..	996	87	208	7	2	927	78	175	3	1
Encephalitis, acute	1	0		0		3	0		0	
Enteric fever:										
Typhoid ..	2	0	0	1		6	0	0	0	1
Paratyphoid ..	2	1	0	0		3	0	5(B)	0	4(B)
Food-poisoning ..	257	72	14	0		146	26	10	4	
Infective enteritis or diarrhoea under 2 years				6	18				10	20
Measles*	14,317	675	636	468	156	3,916	294	147	47	10
Meningococcal infection	22	4	10	0	5	17	3	10	4	1
Ophthalmia neonatorum	30	2	3	0		26	0	9	0	
Pneumonia† ..	320	21	175	10	10	507	34	225	21	7
Poliomyelitis, acute:										
Paralytic ..	16	2	0	0		13	2	0	0	6
Non-paralytic ..	4	2	1			8	0			
Puerperal fever§ ..	212	32	8	2		211	34	5	3	1
Scarlet fever ..	919	64	64	26	21	628	44	83	30	19
Tuberculosis:										
Respiratory ..	630	57	97	16		608	73	135	16	
Non-respiratory	69	9	17	1		93	9	25	3	
Whooping-cough	870	34	68	39	104	655	28	55	16	9

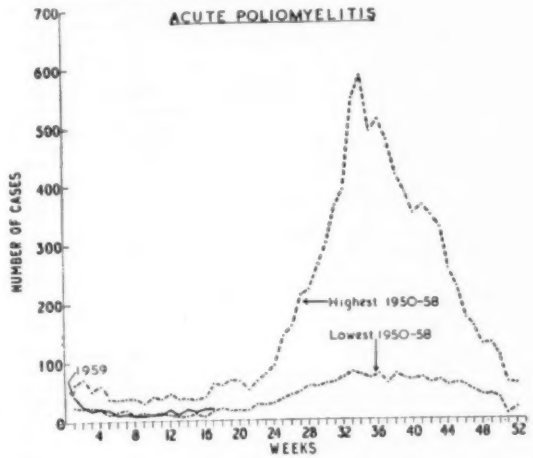
DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	1	0	1	10	0	0	0	0
Influenza	37	2	0	0	3	35	0	4	0	0
Measles		1	0	0			0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	416	37	20	10	12	654	50	23	13	11
Poliomyelitis, acute	0	0		0	0	3	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	73	4	4	1	1	85	3	4	0	6
Non-respiratory		1	1	0	0		2	0	0	1
Whooping-cough	0	0	0	1	0	0	0	0	0	0
Deaths 0–1 year ..	289	38	21	7	12	327	29	33	5	12
Deaths (excluding stillbirths) ..	9,285	759	528	133	166	10,647	772	607	110	185
LIVE BIRTHS ..	14,724	1234	1034	277	406	14,456	1190	1160	248	416
STILLBIRTHS ..	342	31	17			321	24	28		

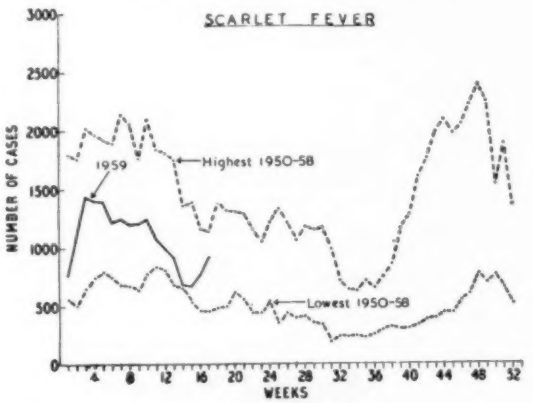
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

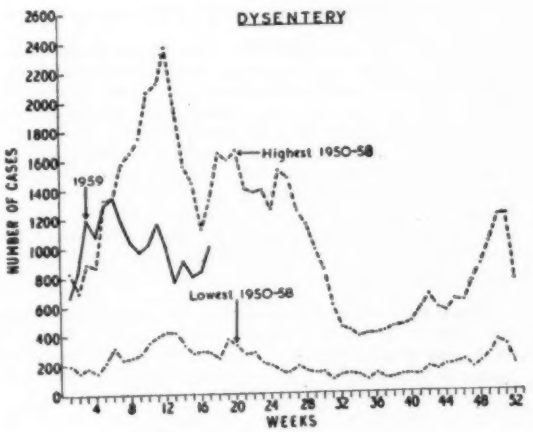
Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ——. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Week Ending May 2

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Apr. 25	Week Ending May 2
Measles		
Durham	1,256	**1,168**
South Shields C.B.	145	**233**
Essex	836	**829**
Harlow U.D.	56	**188**
Gloucestershire	344	**422**
Bristol C.B.	199	**287**
Lancashire	1,401	**1,437**
Liverpool C.B.	115	**150**
Manchester C.B.	217	**234**
Lancaster M.B.	49	**124**
Surrey	795	**751**
Croydon C.B.	197	**221**
Yorkshire West Riding	1,641	**1,541**
Sheffield C.B.	150	**169**
Dysentery		
Essex	14	**64**
Southend-on-Sea C.B.	0	**34**
West Ham C.B.	8	**16**
Kent	21	**25**
Dartford M.B.	0	**15**
Middlesex	35	**48**
Edmonton M.B.	11	**8**
Tottenham M.B.	5	**10**
Nottinghamshire	15	**37**
Nottingham C.B.	5	**16**
Beeston and Stapleford U.D. ...	6	**12**
Worcestershire	19	**27**
Evesham M.B.	13	**25**
Yorkshire West Riding ...	57	**110**
Bradford C.B.	9	**31**
Leeds C.B.	25	**37**
Glamorganshire	51	**62**
Cardiff C.B.	18	**20**
Rhondda M.B.	19	**32**
Acute Poliomyelitis		
London	4	**4**
Lancashire	4	**4**
Yorkshire West Riding	2	**4**
Food-poisoning		
London	85	**72**
Hammersmith	45	**33**

Medical News

Training in Radiation Dangers.—The special postgraduate courses in science and medicine for practitioners in the radiological field recommended by the Veale Committee, which was set up after the accident at Windscale, are expected to be available in London University by October. One will be run by the Royal Marsden Hospital, and the other by the Middlesex and St. Bartholomew's Hospitals, jointly. An announcement made on May 13 by the United Kingdom Atomic Energy Authority says that similar courses may be arranged elsewhere in the country. The Committee is still considering whether a national training centre is desirable.

Conan Doyle Centenary.—Among the unusual items now on view in a small centenary exhibit in the Wellcome Historical Medical Library is an original letter from PAUL EHRLICH in which he tells a medical friend in London of his great interest in CONAN DOYLE and asks him to try to get a signed portrait for him. Sir HENRY DALE recalls that this portrait always hung in EHRLICH'S study. Other interesting exhibits are the *Strand Magazine* with the first story of the series which was to make Sherlock Holmes known all over the world (*A Scandal in Bohemia*, 1891); the illustrated programme of the dramatic version staged in New York in 1900 with WILLIAM GILLETTE as Sherlock Holmes; and portraits of Dr. JOSEPH BELL and Professor RUTHERFORD, who appears as Professor Challenger in Doyle's *Lost World*. (See special article p. 1341.)

Institute of Diseases of the Chest.—The existing laboratories of the Institute of Diseases of the Chest have proved inadequate for the research work on which the staff is now engaged, and a new building has been put up in the grounds of the Brompton Hospital to house some of the research departments. Opening the new laboratories last week, Lord COTTESLOE, chairman of the governing body of the British Postgraduate Medical Federation, described the Institute as an example of British compromise that worked very well, for though the Brompton Hospital was administered by the Ministry of Health and the Institute by London University the work of the two was successfully integrated. The Institute, he said, had established itself as a highly important centre for training research workers and consultants in clinical medicine, and it was attracting graduates from all over the world. Dr. J. G. SCADDING, the dean of the Institute, also spoke at the opening ceremony. He said that much of the research in physiology, morbid anatomy, bacteriology, biochemistry, and allergy was being conducted in co-operation with clinical and laboratory workers in the Brompton and London Chest Hospitals. Important studies of chronic bronchitis were continuing, on the clinical side particularly by Dr. NEVILLE OSWALD, and on the laboratory side by Dr. LYNNE REID, whose work on the morbid anatomy of chronic bronchitis had attracted world-wide attention. Dr. SCADDING also described many other research projects being undertaken at the Institute, and the guests who attended the opening ceremony were able to inspect a variety of informative demonstrations which the staff had prepared for the occasion.

Wellcome Foundation.—Members of the Carlsberg Foundation and the management of the Carlsberg Breweries were entertained to dinner by the Wellcome Foundation at the Fishmongers Hall on May 12, when they had an opportunity of meeting representatives of Government, and men distinguished in science and medicine, in the academic world, and in industry. Sir HENRY DALE, O.M., who was in the chair, said that this was the third such meeting of the leaders of these two great charitable foundations. In his toast to the visiting foundation Sir Henry paid special tribute to Professor NIELS BOHR, "pupil and co-worker, now many years ago in Cambridge, of our own J. J. THOMSON and ERNEST RUTHERFORD." The response to the toast was made by Professor B. JESSEN, chairman of the Carlsberg Foundation. Mr. MICHAEL PERRIN, chairman of the Wellcome Foundation Ltd., proposed the health of the guests, to which Viscount HAILSHAM replied. Professor NIELS BOHR, who received an ovation, recalled an observation made to him by Lord RUTHERFORD that the only person who could take away one's good name was oneself.

College of General Practitioners.—The North-West England Faculty of the College held a symposium on April 26, in Manchester, on "Coronary Artery Disease in General Practice" with Professor ROBERT PLATT, president of the Royal College of Physicians, in the chair. Over 500 general practitioners from the north-west of England attended, and more than 100 applications had to be refused. The speakers included three consultant cardiologists, Dr. EVAN JONES, Dr. C. S. MCKENDRICK, Dr. H. LEMPERT, and two general practitioners, Dr. P. S. BYRNE and Dr. R. GUEST GORNALL.

New Victoria Hospital, Kingston.—There was a response of over £800 in donations and covenanted subscriptions at

an appeal dinner for the New Victoria Hospital on May 12, arranged by the Mayor of Kingston-upon-Thames. The New Victoria Hospital was opened a year ago as a voluntary hospital of 22 beds—the only hospital supported entirely by voluntary effort to be opened since the hospitals were nationalized in 1948. It replaces the old Victoria Hospital, Kingston, originally a general-practitioner hospital, which was converted by the regional hospital board in 1951 into a gynaecological unit. The DUKE OF SUTHERLAND, president of the hospital, presided at the dinner. Mr. A. LAWRENCE ABEL responded to the toast of the hospital proposed by the MAYOR OF KINGSTON-UPON-THAMES.

Chelsea Clinical Society.—LORD BOOTHBY gave a highly entertaining performance when speaking as guest of honour at the annual dinner of Chelsea Clinical Society. But he was able to instruct his hosts as well, for on the eve of the publication of the Hinchliffe Report he had this to say about treatment: "It doesn't matter what you do to your patients, but do something to them. Give them the impression that you are up and about. Make them feel there is a bustle going on." Lord Boothby added that he regarded his successful parliamentary fight for the retention of heroin as one of the two positive achievements of his political career. After Sir HENEAGE OGILVIE had proposed the toast to the guests and Dr. T. F. Fox had replied, Dr. HARRY COKE, the outgoing president of the Society, installed Dr. G. T. PITTS as the new president. Dr. Coke had previously described the flourishing state of the Society, which now has 299 members out of a total of 300 permitted by the Society's rules.

Advertising Inquiry Committee.—The medical panel of this committee, under the chairmanship of Dr. DESMOND O'NEILL, has submitted a report to the MINISTER OF HEALTH. Mr. Walker-Smith, which emphasizes the dangers of free availability of non-scheduled drugs, and suggests that a study should be made of the extent to which "self-medication" is a social problem in this country. One of the activities of the Advertising Inquiry Committee, formed early this year under the chairmanship of Sir HENRY TURNER, has been an inquiry into the advertising of medical and para-medical products. The address of the Committee is 49, Cresswell Place, London, S.W.1.

Dublin University.—Professor R. J. V. PULVERTAFT, professor of clinical pathology at Westminster Hospital School of Medicine, has been appointed John Mallet Purser Lecturer for 1959.

Professor W. C. W. Nixon, director of the obstetric unit at University College Hospital, has been appointed consultant in obstetrics and gynaecology to the University of Ceylon for the month of June to August inclusive.

COMING EVENTS

National Marriage Guidance Council.—The twenty-first birthday year annual conference on "Parenthood" will be held at the Palace Hotel, Buxton, Derbyshire, from May 28 to 31. Application forms and details from the Office Secretary, National Marriage Guidance Council, 78, Duke Street, Grosvenor Square, London, W.1.

"Cours de Perfectionnement d'Endocrinologie."—The twelfth course will be held at Hôpital Laënnec from June 21 to 27. Details from Secrétariat du Service du Docteur Albeaux-Fernet, Hôpital Laënnec, 42, rue de Sèvres, Paris, 7.

American College of Chest Physicians.—The second Spanish national meeting will be held at Valencia (Spain) from June 29 to July 1. Details from Dr. A. CARALPS, American College of Chest Physicians in Spain, Corcega, 393, Barcelona, Spain.

Indian Medical Service Dinner Club.—The annual dinner will be held at the East India and Sports Club Limited, St. James's Square, London, S.W.1, on June 12. Tickets and information from the Secretary of the I.M.S. Dinner Club, Medical Board Room, Commonwealth Relations Office, Matthew Parker Street, London, S.W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ● Application should be made first to the institution concerned.

Monday, May 25

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. P. Wade: Radiotherapy of Malignant Skin Conditions (II).

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University Medical School, 9 p.m., Presidential Address by Dr. N. P. Chamarette: Some Views on the Theory and Function of Dreams.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. L. E. Glynn: Role of Auto-immunity in Diseases of Connective Tissue.

Tuesday, May 26

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. I. Williams: Cutaneous Manifestations of Venereal Disease.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Mr. A. Walker: Maternal Mortality 1952-1954.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Small Lecture Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., annual general meeting. Dr. J. C. McDonald: Value of Periodic Health Examinations.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. George Bonney: Backache in Women.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. Colin Edwards: Neurology.

Wednesday, May 27

CHELMSFORD CLINICAL SOCIETY.—At Chelmsford and Essex Hospital, 8.30 p.m., Dr. Griffith Pugh: Man in Antarctica. Members of the B.M.A. are invited to attend.

HARVEIAN SOCIETY OF LONDON.—At Zoological Society's Rooms, Regent's Park, London, N.W., 8.15 p.m., Buckston Browne-Gray Hill dinner.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Moniliasis as a Problem of Diagnosis and Treatment.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Paul Wood: Further Studies of Atrial Septal Defect.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Manchester University Medical School, 5 p.m., Dr. R. W. Fairbrother: Prevention and Control of Staphylococcal Infection.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor R. J. V. Pulvertaft: Films on Toxoplasmosis and Leishmania.

Thursday May 28

HONYMAN GILLESPIE LECTURE.—At Anatomy Theatre, University New Buildings, Edinburgh, 5 p.m., Dr. A. R. Currie: Dynamic Approach to Human Endocrine Pathology.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. Mattingly: Rheumatic Aspects of Cutaneous Disease.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. Hugh Gainsborough: Diabetes and Diabetics.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. E. Pochin: Therapeutic Use of Radioiodine.

ROYAL NORTHERN HOSPITAL.—2.45 p.m., Dr. Michael Peters: Some Pathological Specimens (demonstration).

Friday, May 29

INSTITUTE OF CHILD HEALTH.—5 p.m., Professor S. Van Creveld (Amsterdam): Myocarditis in Childhood.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. O. L. S. Scott.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5 p.m., Dr. Barry J. Anson (Chicago): Development and Adult Anatomy of the Auditory Ossicles in Relation to Certain Problems in Endaural Surgery.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. I. S. Smillie: Injuries of the Knee.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Special Lecture by Dr. Barry Anson: Development and Adult Anatomy of the Auditory Ossicles in Relation to Certain Problems in Endaural Surgery.

MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, near Birmingham.—8 p.m., Professor O. L. Zangwill: Some Problems of Cerebral Dominance.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Browne.—On May 5, 1959, to Muriel James, M.B., wife of Dr. D. Warren Browne, of Chichester and Bognor Regis, Sussex, a son.

Searle.—On May 9, 1959, at St. Mary's Hospital, Portsmouth, Hants, to Dr. Gwenllian Searle (formerly Edwards), wife of Dr. J. S. T. Searle, a sister for Anne.

Sers.—On April 1, 1959, in Antigonish, Nova Scotia, to Drs. Phyllis (formerly Neil) and Rolf Sers, a sister for Robert and Larissa—Barbara Elizabeth.

Smith.—On March 30, 1959, in Nairobi, to Dorothy (formerly White), M.B., Ch.B., D.Obst.R.C.O.G., and Ronald Smith, a son—David Michael Ewing.

Whyte.—On May 2, 1959, at Much Wenlock Hospital, Shropshire, to Drs. Ursula (formerly Kynoch) and George Whyte, a son—Donald.

DEATHS

Andrew.—On April 25, 1959, at Reigate, Surrey, John Andrew, M.R.C.S., L.R.C.P., of 56, Grand Avenue, Worthing, Sussex.

Chenard de la Giraud.—On April 25, 1959, at Kumasi, Ghana, Arthur Henri Chenard de la Giraud, M.R.C.S., L.R.C.P., aged 53.

Davies.—On April 23, 1959, at Lymington Hospital, Lymington, Hants, Stuart Thomas Davies, M.R.C.S., L.R.C.P., Lieutenant-Colonel, I.M.S. (retired), aged 57.

Latimer.—On April 25, 1959, Gordon Dill Latimer, M.B., B.Ch., of "Northcote," Ripon, Yorks.

Marsh.—On April 20, 1959, at Guy's Hospital, London, S.E., Henry Rupert Marsh, M.R.C.S., L.R.C.P., of Crit Hall Gate, Benenden, Kent.

Seaton.—On April 19, 1959, in hospital, John Stewart Seaton, L.R.C.P.&S.Ed., L.R.F.P.S., of Pine Lodge, Stanley Avenue, Bebington, Cheshire.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Dyspareunia After Hysterectomy

Q.—*Is dyspareunia common after vaginal hysterectomy, owing to shortening of the vagina? Could this complication also arise from an abdominal hysterectomy?*

A.—Unless an unusually large cuff of vagina is removed, either unnecessarily or as part of a radical operation for malignant disease, total hysterectomy by either abdominal or the vaginal route does not materially shorten the vagina. Tenderness of the scar in the vaginal vault is also quite exceptional. Hysterectomy should not, therefore, by itself cause dyspareunia. It has to be recognized, however, that a decision to remove the uterus vaginally is often prompted by the presence of some form of prolapse. The excision of an enterocele and the strengthening of the vaginal vault may then result in narrowing of the upper vagina and thus make it functionally shorter. Added to that, many surgeons always carry out posterior colpoperineorrhaphy when vaginal hysterectomy is performed. This is a traditional procedure which is probably unnecessary in most cases and is much more likely to cause dyspareunia than the hysterectomy itself.

Many other factors enter the picture. The type of prolapse for which vaginal hysterectomy is sometimes performed is caused in part by congenital shortness of the vagina. The operation then tends to be blamed for what was pre-existent. Hysterectomy and vaginal repair operations are most often carried out on women at or approaching the menopause, at a time when climacteric atrophy is about to reduce vaginal capacity and when advancing years may be curbing the sexual appetite of either husband or wife. Sometimes the operation is used as an excuse to avoid intercourse. Often the couple are left in ignorance of the implications of the operation and they fear that coitus will cause harm. If intercourse is attempted too early after the operation anxiety and tenderness cause vaginismus. If it is attempted too late climacteric atrophy may have intervened to cause difficulty. In either case the occurrence of dyspareunia deters further attempts and the situation comes to be regarded as hopeless.

The resumption of comfortable coitus following hysterectomy therefore depends on: (i) The avoidance of unnecessary additional procedures which narrow the vagina unduly. When colporrhaphy has to be performed as well allowance should be made for subsequent senile atrophy of the vagina. (ii) Explanation of the significance of the operation to both husband and wife. (iii) Observation of the patient for several weeks after operation so that she can be specifically told when to resume coitus and how to overcome vaginismus or other difficulty which may be encountered initially.

Familial Periodic Paralysis

Q.—*What is the treatment for familial periodic paralysis? Is potassium helpful, and if so in what dose?*

A.—Attacks of familial periodic paralysis may be precipitated in some patients by a high carbohydrate intake and by excessive physical exertion, and it is obviously wise to avoid these precipitating factors. The relationship between the plasma potassium level and the development of an attack of paralysis is not thoroughly understood, but in a number of cases the plasma potassium level is reduced during an attack and normal in the intervals between attacks, while in a few cases normal plasma potassium levels have been recorded during attacks. In patients in whom an attack is accompanied by a low plasma potassium level it is reasonable to give potassium chloride 1 g. eight-hourly by the mouth with the object of preventing attacks, but in such a rare disease, in which attacks may occur at very infrequent intervals, it is difficult to assess the efficiency of this treatment.

Vitreous Haemorrhage

Q.—*Is there any new treatment for vitreous haemorrhages?*

A.—Many new forms of treatment for vitreous haemorrhages have been tried in recent years, but the results are disappointing. In most cases a small vitreous haemorrhage which is not associated with serious intra-ocular disease absorbs spontaneously.

NOTES AND COMMENTS

"H3."—Dr. H. B. WRIGHT (Mount Merrion, Co. Dublin) writes: I was very interested to read the reply about H3 ("Any Questions?" March 28, p. 872), having asked a similar question a couple of years ago with reference to Parkinsonism. Personally, from limited experience of it, I do feel this substance helps in Parkinsonism. Unfortunately, owing to the irregular receipt of generous supplies sent to me gratis from the Institute in Bucharest, I was unable to make any scientific comparisons. Delivery got held up all along the postal line for all sorts of reasons; many boxes seemed to get lost, and the mere mention of the contents being anything to do with procaine was sufficient to excite the departments of excise everywhere. Eventually I grew tired of the endless correspondence and explanations (it was not exactly rejuvenating) and I gave up my treatment. I hear the supply position is easier now, and I should be interested to hear if any of your readers have any similar impressions about its use in Parkinsonism. Its use in rejuvenation is best left to those who live to kiss the feet of Ayesha.

OUR EXPERT replies: A beneficial effect of procaine in Parkinsonism has occasionally been mentioned in the literature. The reports have occurred at two periods: about 1947–52 in America (e.g., Graubard and Peterson[1]), when intravenous procaine was in vogue for the treatment of many painful conditions, and again recently in Rumania and Germany, where H3 is being used to treat diseases of old age. The disappearance of tremor after giving H3 has also been reported.[2] Usually one or two cases have been described among a large group of patients with miscellaneous diseases receiving the same treatment, and no attempt seems to have been made to carry out a controlled assessment of its effectiveness. Doshay,[3] who does not include procaine among the many drugs which have a place in the treatment of Parkinsonism, points out that the symptoms often improve if emotional tension is reduced.

REFERENCES
1 Graubard, D. J., and Peterson, M. C., *Anesthesiology*, 1949, **10**, 175.
2 Odens, M., *Lancet*, 1959, **1**, 737.
3 Doshay, L. J., *Parkinsonism and Its Treatment*, 1954. Philadelphia.

Correction.—In the article on "Breast Abscess" by Mr. I. C. S. Knight and Mr. B. Nolan (May 9, p. 1224) the dose of stilboestrol (line 7, p. 1226) should have been given as 15 mg. three times a day (not 45 mg.).

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.).
Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 30 1959

HYPERTENSION—TREATED AND UNTREATED

A STUDY OF 400 CASES

BY

A. W. D. LEISHMAN, M.A., D.M., F.R.C.P.

Consulting Physician, United Sheffield Hospitals

The present preoccupation of our profession with the lowering of blood pressure must inevitably defeat any future attempt to study the natural history of hypertensive disease, but in view of the attention this topic has already received this may not be counted altogether a misfortune. Nevertheless, as Simpson and Gilchrist (1958) point out, it is particularly during the next few years that there is likely to be felt the need for a satisfactory yardstick against which the long-term success of modern hypotensive treatment can be measured.

There are, of course, available to-day a number of admirable studies of untreated hypertension. Yet it is doubtful if any of these can be regarded as fully satisfying this requirement since they suffer in common the disadvantage of all retrospective studies that the picture presented is insufficiently detailed. It therefore seemed that this might be an appropriate moment to give a further report on the group of untreated hypertensive patients whose year-to-year progress from 1946 onwards was the subject of an earlier communication (Leishman, 1953). On this occasion, however, it was felt that the time had come to employ this "control" series of untreated cases for the purpose originally intended, since there were now available for comparison two further groups of patients treated respectively by lumbo-dorsal sympathectomy and by ganglion-blocking drugs.

Since regular observation of all three groups (a total of 402 patients) has been continuing simultaneously, it was hoped that comparison of their respective welfare or fate would by this stage provide a fair evaluation of these methods of treatment.

Untreated Hypertension

The decision taken in 1946 to follow by annual examination every hypertensive patient under the age of 60 who either declined or was considered unsuitable for sympathectomy (the only effective treatment then available) was prompted solely by the desire to learn more about the natural prognosis of this disease. Altogether 211 patients (87 men, 124 women) with diastolic pressure initially not less than 100 mm. Hg have now been followed in this way up to the present time or until their death. Since the object was to collect rather than select cases, all grades of hypertension are represented, and, as is later shown, this group does not appear to have been unduly weighted by cases of exceptional severity. One-half (106) of these patients are now dead, and this number represents 66% of the men and 39% of the women who with the exception of 14 have all died before they were 60. The age and period of observation of every case is recorded in Figs. 1 to 5 together with the individual causes of death as accurately as these could be ascertained. It may, however, be noted that the use of the term C.V.A. (cerebral vascular accident) has been necessary on occasions when post-mortem evidence was lacking or the clinical details supplied were insufficient to justify a diagnosis of cerebral haemorrhage; also that when uraemia complicated terminal heart failure this has been recorded as a cardiac death.

Prognostic Considerations

When the behaviour of these patients was earlier studied the clinical features which then appeared to have been especially unfavourable were listed as male sex, high diastolic pressure, albuminuria, retinopathy, abnormal electrocardiograms, and possibly absence of obesity; and when revised to-day, after an opportunity of five years' further observation, this list appears to need only minor amendment. Certainly it requires only a glance at the mortality rates shown in Fig. 6 to appreciate the hazard both of being male and of having a high diastolic pressure, since not a single man survives to-day whose diastolic pressure initially exceeded 130

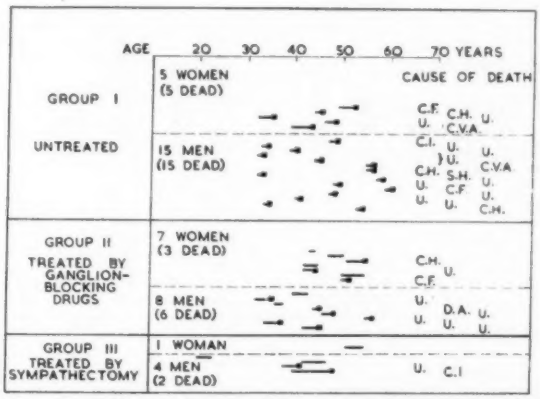

FIG. 1.—Malignant hypertension. (Criterion—papilloedema.) B.A.T.=Basilar artery thrombosis. C.F.=Congestive failure. C.H.=Cerebral haemorrhage. C.I.=Cardiac infarct. C.V.A.=Cerebral vascular accident. D.A.=Dissecting aneurysm. R.A.=Ruptured aorta. S.H.=Subarachnoid haemorrhage. U.=Uraemia.

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Q.—*Is dyspareunia common after vaginal hysterectomy, owing to shortening of the vagina? Could this complication also arise from an abdominal hysterectomy?*

A.—Unless an unusually large cuff of vagina is removed, either unnecessarily or as part of a radical operation for malignant disease, total hysterectomy by either abdominal or the vaginal route does not materially shorten the vagina. Tenderness of the scar in the vaginal vault is also quite exceptional. Hysterectomy should not, therefore, by itself cause dyspareunia. It has to be recognized, however, that a decision to remove the uterus vaginally is often prompted by the presence of some form of prolapse. The excision of an enterocele and the strengthening of the vaginal vault may then result in narrowing of the upper vagina and thus make it functionally shorter. Added to that, many surgeons always carry out posterior colpoperineorrhaphy when vaginal hysterectomy is performed. This is a traditional procedure which is probably unnecessary in most cases and is much more likely to cause dyspareunia than the hysterectomy itself.

Many other factors enter the picture. The type of prolapse for which vaginal hysterectomy is sometimes performed is caused in part by congenital shortness of the vagina. The operation then tends to be blamed for what was pre-existent. Hysterectomy and vaginal repair operations are most often carried out on women at or approaching the menopause, at a time when climacteric atrophy is about to reduce vaginal capacity and when advancing years may be curbing the sexual appetite of either husband or wife. Sometimes the operation is used as an excuse to avoid intercourse. Often the couple are left in ignorance of the implications of the operation and they fear that coitus will cause harm. If intercourse is attempted too early after the operation anxiety and tenderness cause vaginismus. If it is attempted too late climacteric atrophy may have intervened to cause difficulty. In either case the occurrence of dyspareunia deters further attempts and the situation comes to be regarded as hopeless.

The resumption of comfortable coitus following hysterectomy therefore depends on: (i) The avoidance of unnecessary additional procedures which narrow the vagina unduly. When colporrhaphy has to be performed as well allowance should be made for subsequent senile atrophy of the vagina. (ii) Explanation of the significance of the operation to both husband and wife. (iii) Observation of the patient for several weeks after operation so that she can be specifically told when to resume coitus and how to overcome vaginismus or other difficulty which may be encountered initially.

Familial Periodic Paralysis

Q.—*What is the treatment for familial periodic paralysis? Is potassium helpful, and if so in what dose?*

A.—Attacks of familial periodic paralysis may be precipitated in some patients by a high carbohydrate intake and by excessive physical exertion, and it is obviously wise to avoid these precipitating factors. The relationship between the plasma potassium level and the development of an attack of paralysis is not thoroughly understood, but in a number of cases the plasma potassium level is reduced during an attack and normal in the intervals between attacks, while in a few cases normal plasma potassium levels have been recorded during attacks. In patients in whom an attack is accompanied by a low plasma potassium level it is reasonable to give potassium chloride 1 g. eight-hourly by the mouth with the object of preventing attacks, but in such a rare disease, in which attacks may occur at very infrequent intervals, it is difficult to assess the efficiency of this treatment.

Vitreous Haemorrhage

Q.—*Is there any new treatment for vitreous haemorrhages?*

A.—Many new forms of treatment for vitreous haemorrhages have been tried in recent years, but the results are disappointing. In most cases a small vitreous haemorrhage which is not associated with serious intra-ocular disease absorbs spontaneously.

NOTES AND COMMENTS

"H3."—Dr. H. B. WRIGHT (Mount Merrion, Co. Dublin) writes: I was very interested to read the reply about H3 ("Any Questions?" March 28, p. 872), having asked a similar question a couple of years ago with reference to Parkinsonism. Personally, from limited experience of it, I do feel this substance helps in Parkinsonism. Unfortunately, owing to the irregular receipt of generous supplies sent to me gratis from the Institute in Bucharest, I was unable to make any scientific comparisons. Delivery got held up all along the postal line for all sorts of reasons; many boxes seemed to get lost, and the mere mention of the contents being anything to do with procaine was sufficient to excite the departments of excise everywhere. Eventually I grew tired of the endless correspondence and explanations (it was not exactly rejuvenating) and I gave up my treatment. I hear the supply position is easier now, and I should be interested to hear if any of your readers have any similar impressions about its use in Parkinsonism. Its use in rejuvenation is best left to those who live to kiss the feet of Ayesha.

OUR EXPERT replies: A beneficial effect of procaine in Parkinsonism has occasionally been mentioned in the literature. The reports have occurred at two periods: about 1947-52 in America (e.g., Graubard and Peterson[1]), when intravenous procaine was in vogue for the treatment of many painful conditions, and again recently in Rumania and Germany, where H3 is being used to treat diseases of old age. The disappearance of tremor after giving H3 has also been reported.[2] Usually one or two cases have been described among a large group of patients with miscellaneous diseases receiving the same treatment, and no attempt seems to have been made to carry out a controlled assessment of its effectiveness. Doshay,[3] who does not include procaine among the many drugs which have a place in the treatment of Parkinsonism, points out that the symptoms often improve if emotional tension is reduced.

REFERENCES

1 Graubard, D. J., and Peterson, M. C., *Anesthesiology*, 1949, **10**, 178.
2 Odens, M., *Lancet*, 1959, **1**, 737.
3 Doshay, L. J., *Parkinsonism and Its Treatment*, 1954. Philadelphia.

Correction.—In the article on "Breast Abscess" by Mr. I. C. S. Knight and Mr. B. Nolan (May 9, p. 1224) the dose of stilboestrol (line 7, p. 1226) should have been given as 15 mg. three times a day (not 45 mg.).

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